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STAPHYLOCOCCIC PNEUMONIA OCCURRING DURING AN EPIDEMIC OF INFLUENZA

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During the late fall and early winter of 1940-1941 an epidemic of influenza involved most sections of the United States, as well as the Hawaiian Islands, Puerto Rico and probably many other areas.[1] Virus isolations during the acute phase and immunologic studies of acute and convalescent phase serums on patients from widely scattered localities indicated that the virus of influenza A was by far the predominant, if not the only, one of the known viruses implicated in the epidemic.[2] If one

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1. (*a*) Prevalence of Communicable Diseases in the United States: December 1-28, 1940, Pub. Health Rep. **56**:89-92 (Jan. 17) 1941. (*b*) Prevalence of Communicable Diseases in the United States: December 29, 1940–January 25, 1941, ibid. **56**:259-264 (Feb. 14) 1941. (*c*) Prevalence of Communicable Diseases in the United States: January 26–February 22, 1941, ibid. **56**:481-485 (March 14) 1941.

2. Sulkin, S. E.; Bredeck, J. F., and Willett, J. C.: A Study of Epidemic Influenza, with Special Reference to the 1940-41 Outbreak in St. Louis, J. Missouri State M. A., March 1941, pp. 71-75. (*b*) Dalldorf, G.; Whitney, E., and Ruskin, A.: A Controlled Clinical Test of Influenza A Vaccine, J. A. M. A. **116**:2574-2577 (June 7) 1941. (*c*) Lennette, E. H.; Rickard, E. R.; Hirst, G. K., and Horsfall, F. L., Jr.: The Diverse Etiology of Epidemic Influenza, Pub. Health Rep. **56**:1777-1788 (Sept. 5) 1941. (*d*) Brown, J. W.; Eaton, M. D.; Meiklejohn, G.; Lagen, J. B., and Kerr, W. J.: An Epidemic of Influenza: Results of Prophylactic Inoculation of a Complex Influenza A-Distemper Vaccine, J. Clin. Investigation **20**:663-669 (Nov.) 1941. (*e*) Pearson, H. E.; Eppinger, E. C.; Dingle, J. H., and Enders, J. F.: A Study of Influenza in Boston During

(Footnote continued on next page)

judges from the available reports, the disease generally was mild and pulmonary complications were neither frequent nor severe.

The epidemic reached Boston late in December and persisted throughout January; most cases of the disease occurred during the first two weeks of the latter month. The clinical features of some of the uncomplicated cases, along with the results of virus isolations and immunologic studies, have been reported by Pearson, Eppinger, Dingle and Enders.[2e] In the course of the epidemic in Boston an unusually large number of cases of staphylococcic pneumonia were encountered as a complication of influenza. The more important clinical and laboratory data in these cases will be presented here. A more detailed description of the pathologic observations in 8 of the cases included here is given elsewhere.[3] In a recent paper from another Boston hospital, the literature was reviewed and 5 cases were reported which are similar to some of those to be described here.[4] Serologic evidence of infection with influenza A virus was obtained in 3 of those cases. Four fatal cases were also reported from North Carolina.[5]

CLINICAL MATERIAL

In all of the cases included in this report the patients were over 14 years of age and were treated at the Boston City Hospital, with the exception of 2 in which the patients were treated elsewhere and which are included because they were of especial interest. In every patient Staphylococcus aureus was obtained as the only or the predominant organism from one or more cultures of sputum or from the lungs, or it was obtained in pure culture from blood or from pleural or other exudates or from multiple sources. Virus studies were carried out only in a few of these cases, and the results have been included in the report by Pearson and associates.[2e] Thorough bacteriologic studies were not carried out on all of the patients admitted to the hospital with infection of the respira-

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the Winter of 1940-1941, New England J. Med. **225**:763-770 (Nov. 13) 1941. (*f*) Sulkin, S. E.; Smith, J. E., and Douglass, D. D.: Experimental Study of an Institutional Outbreak of Epidemic Influenza, J. Infect. Dis. **69**:278-284 (Nov.-Dec.) 1941. (*g*) Siegel, M.; Muckenfuss, R. S.; Schaeffer, M.; Wilcox, H. L., and Leider, A. G.: A Study in Active Immunization Against Epidemic Influenza and Pneumococcus Pneumonia at Letchworth Village: IV. Results in an Epidemic of Influenza A in 1940-41, Am. J. Hyg. **35**:186-230 (March) 1942. (*h*) Hare, R.; Auger, W. J., and McClelland, L.: Studies on Influenza: Antibody Level; Isolation of Virus, Canad. Pub. Health J. **33**:72-78 (Feb.) 1942.

3. Wollenman, O. J., Jr., and Finland, M.: Pathology of Staphylococcal Pneumonia Complicating Clinical Influenza, Am. J. Path., to be published.

4. Michael, M., Jr.: Staphylococcus Aureus Pneumonia, with Special Reference to Its Occurrence as a Complication of Influenza, J. A. M. A. **118**:869-874 (March 14) 1942.

5. Baker, R. D.: Staphylococcal Pneumonia During Epidemic Influenza in North Carolina (1941), South. M. J. **35**:240-247 (March) 1942.

tory tract during this period, so that many cases with similar clinical features are not included. This presentation is limited to the cases in which adequate bacteriologic data were obtained.

All of the Staphylococcus strains were classified as Staph. aureus and gave a positive coagulase reaction. Additional studies were made with sixteen of the strains, including eleven from sputum, three from pleural fluid and two from abscesses of the lung. All of them fermented trehalose and mannitol. Uniform suspensions showed more marked agglutination and in higher dilutions in group A serums than in group B serums.[6] The strains varied considerably in the production of alpha and beta toxins, and they probably produced little or no leukocidin, although results of tests for this substance were not conclusive. Mouse inoculation of sputum was not carried out in most instances, because pneumococci were rarely identified in the direct (Neufeld) sputum typings and smears stained with Gram's stain showed abundant organisms resembling staphylococci. In 19 cases, however, sputum which yielded Staphylococcus as the only or the predominant organism in direct cultures was also inoculated into mice. The sputum strains of Staphylococcus in 10 cases proved virulent for mice when given in this manner, while those in the other 9 cases proved totally avirulent. The latter 9 cases included 3 in which Staph. aureus was predominant in cultures of the lungs made at autopsy, 3 in which pure cultures of this organism were obtained from purulent pleural fluid, 1 in which a large staphylococcic pulmonary abscess was evacuated surgically, 1 in which the blood culture was positive for Staph. aureus and 1 in which the organism was obtained only from sputum.

The onset of influenza-like symptoms in every case in which the date could be elicited occurred between December 20 and January 18, and in more than three fourths of the cases it occurred between December 25 and January 12. Symptoms suggesting pulmonary infection began on the same day as those of the influenza in about one third of the cases and within five days in another third of the cases, while in the rest they were delayed six days to three weeks. The extent and severity of the pulmonary involvement varied markedly in different cases. In order to bring out the wide variety of clinical features presented in these cases, we have divided them into six main groups, each of which includes a number of cases with more or less distinctive features. For purposes of brevity the important details in three of the groups of cases are presented in tables 1, 2 and 3; the general characteristics of each group will be summarized in the text.

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6. Julianelle, L. A., and Wieghard, C. W.: The Immunological Specificity of Staphylococci: I. Occurrence of Serological Types, J. Exper. Med. **62**:11-22 (July) 1935.

ACUTE RAPIDLY FATAL PNEUMONIA (TABLE 1)

In the first group there were 7 cases, in all of which the patients had a more or less fulminating pneumonia following symptoms of moderate or severe influenza. Five patients were in their forties; 1 was 19, and the other, 65. In 1 case (7) the symptoms of pneumonia and of influenza began almost simultaneously; in 4 other cases the patients had been ill with influenza for two to four days without improvement when the pneumonia began, while in 2 cases (1 and 5) the patients had been afebrile for three and nine days, respectively, after the influenza. At the time when the pneumonia was presumed to begin the patients had an abrupt recurrence and marked exacerbation of their prostration, which rapidly changed to a state of semistupor and was associated with severe and increasing dyspnea and cyanosis. The temperature at this stage varied from 100 to 105 F.; the pulse rate, from 120 to 160 per minute, and respirations, from 30 to 40 or more per minute. The latter were usually rapid and shallow, but sometimes they were markedly irregular. Signs in the lungs were minimal at first and consisted then mostly of scattered sibilant and sonorous rales, but as the dyspnea and air hunger increased, showers of consonating rales were heard and there appeared scattered areas of consolidation, which seemed to spread and involve most of the lungs. The patients became apathetic, then stuporous and semicomatose and assumed a "livid" appearance. The leukocyte count in case 1 was 800 on two occasions; in the other cases it varied between 6,100 and 14,000. Death occurred within five days after the onset of the pneumonia in 6 cases and on the ninth day in 1 case.

In 2 cases pleuritic pain was an early and prominent symptom. In both of these cases signs of fluid developed, which was later demonstrated, either by thoracentesis or at autopsy, and found to be infected with staphylococci. The sputum in all the cases was usually raised with difficulty and was scant, thick, purulent and either streaked or diffusely tinged with blood. In case 6 a fibrinous, gray-green, blood-streaked mass of sputum was raised which resembled a diphtheritic membrane but which yielded an abundant growth of Staph. aureus in pure culture.

Autopsies were performed in 4 of the 7 cases.[3] All showed diffuse necrotizing bronchitis and bronchiolitis with numerous small and confluent abscesses around the bronchi and massive confluent areas of hemorrhagic and edematous bronchopneumonia. In case 1 the process was more acute and involved mostly the lower and the middle lobe of the right lung, and no abscesses were recognized grossly. Histologically, however, there were edema and necrosis of bronchial and alveolar walls, although the exudate contained little fibrin and few inflammatory cells. Masses of cocci were seen in the necrotic areas in all of these

TABLE 1.—*Relevant Data in Seven Cases of Fatal Acute Staphylococcic Pneumonia Complicating Influenza*[4]

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Case No.	Sex and Age, Yr.	Dates: Hospital Admission	Dates: Onset of Influenza	Dates: Onset of Pneumonia	Dates: Death	Bacteriologic Data: Sputum	Bacteriologic Data: Blood	Bacteriologic Data: Other Sources	Chemotherapy: Drug	Chemotherapy: Gm.	Comment on Clinical Course and Autopsy †
1‡	♀ 46	1/9 1 a.m.	1/3	1/8 10 a.m.	1/9 3:30 p.m.	1/9, G+ cocci	1/9, 0	HB, 0; LL, RL and RU, SA	ST	8	WBC 800; fulminating course, increasing dyspnea, cyanosis, stupor; autopsy: acute hemorrhagic and edematous confluent bronchopneumonia, mostly RL and RM, with emphysematous blebs; ? hyaline alveolar membrane; necrotic alveolar and bronchiolar walls and cocci, bone marrow hyperplasia (granulocytes)
2	♀ 43	1/11 4 a.m.	1/7	1/9	1/13 1 a.m.	1/11, SH; 1/12, SA (no SH)	1/11, SH	HB and Per, 0; liver and spleen, SA; RL and abs. LL, SA; LL and PF, SH and SA	ST NaSD SD	8 5 5	WBC 14,000; increasing dyspnea, cyanosis and pulmonary involvement; autopsy: all lobes with acute necrotizing bronchitis and bronchiolitis and alveolitis, miliary abscesses mostly peribronchial but some confluent, scattered hemorrhage and edema and cocci; virus influenza A in lung (indirect); 1/11, CFA 1:16
3	♂ 46	1/13 10 p.m.	1/9	1/13 a.m.	1/16 6 p.m.	1/16, SA, few SV	1/14, 0	HB, 0; RL and LL, SA, few SV	ST	7	WBC 6,300; mild diabetes, controlled with insulin; increasing prostration, dyspnea, cyanosis, pulmonary consolidation; autopsy: same as case 2
4	♂ 65	1/13 9 p.m.	1/6	1/9	1/14 2 p.m.	..	1/13, 0	Lung, PF and Per, SA	ST	7	Dyspnea, pleurisy, cyanosis, restlessness, increasing air hunger; autopsy: 700 cc. turbid yellow fluid in right pleura, 75 cc. in pericardium, myocardial hypertrophy (400 Gm.), healing pulmonary infarct RU, congestion of liver; lungs as in case 2
5	♂ 49	1/12 11 p.m.	12/30	1/12 5 p.m.	1/14 9 p.m.	1/13, SA, few SV	1/13, SA 1/14, SA	.....	SD	12	WBC 12,000; improvement after 3 days' "flu"; sudden prostration, cough, sore throat, pleurisy on left side, friction rub LL, consolidation extending through LL, LU and RL; increasing dyspnea, cyanosis and stupor; no autopsy
6	♀ 19	1/4 1 p.m.	12/31 11 p.m.	1/2 7 p.m.	1/6 10 a.m.	1/5, SA (twice)	1/4, 0	.....	NaSD SD	5 9	WBC 6,100; chills, irregular labored respiration, hoarseness, presternal pain, rose-colored fibrinopurulent sputum, bronchitis and bronchiolitis; increasing cyanosis, air hunger and pulmonary consolidation; no autopsy
7	♂ 48	12/28 5 a.m.	12/22	12/22	12/31 4 p.m.	12/28, SA 12/30, SA 12/31, SA	12/28, 0 12/29, 0 12/30, 0	12/30, PF, SA	SP	14	WBC 13,700; chills, fever, pleurisy on left side; scattered musical and crepitant rales; 10 cc. purulent pleural fluid by thoracentesis; increasing dyspnea, cyanosis and "collapse"; no autopsy

* The following abbreviations are used throughout tables 1, 2 and 3: G+, gram-positive; SA, Staph. aureus; SH, Streptococcus haemolyticus; SV, Str. viridans (or alpha hemolytic streptococci); 0, no growth in a culture; HB, heart blood; LL, lower lobe of the left lung; LU, upper lobe of the left lung; RL, lower lobe of the right lung; RM, middle lobe of the right lung; RU, upper lobe of the right lung; abs., abscess; PF, pleural fluid; Per., pericardial fluid; ST, sulfathiazole; NaSD, sodium sulfadiazine; SD, sulfadiazine; SP, sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine); WBC, leukocytes per cubic millimeter, and CFA, complement fixation test with influenza A virus (serum dilution).[2e]

† For more detailed autopsy observations in cases 1 through 4, see the corresponding case numbers in the paper by Wollenman and Finland.[3]

‡ Drs. George E. Currier, Sidney C. Dalrymple and Dwight O'Hara, of Waltham Hospital, gave us permission to report the data in case 1.

cases. Hyaline-like membranes similar to those described in the influenzal pneumonias of 1918 [7] were seen, particularly in case 1.

Staph. aureus was the only or the predominant organism obtained from the various cultures made during life and at autopsy. Small numbers of Streptococcus viridans were also obtained in 2 cases. In case 2 the first cultures of sputum and of blood showed hemolytic streptococci, but on the following day only staphylococci were obtained from the sputum. At autopsy in this case culture of heart blood showed no growth. Staphylococci were grown alone from some sites and with hemolytic streptococci from others (table 1). In the microscopic sections of the lungs, chains of cocci were seen in some hemorrhagic and edematous areas of intact alveoli, while masses of cocci were seen in abundance in the necrotic areas. Ferret inoculation of a suspension of lung in this case yielded strong presumptive evidence of the presence of influenza A virus.[2e]

FATAL ORGANIZING AND FIBROSING PNEUMONIA (TABLE 2 AND FIGS. 1 AND 2)

In a second group of 6 cases the patients had a clinical course similar to that in the first group except that the patients survived from fifteen to fifty-six days after the onset of severe pulmonary symptoms. In all of these cases the patients were 50 years of age or older, and in 3 they were over 70. The pneumonia began almost simultaneously with the influenza in 4 cases, but in 1 the patient apparently enjoyed a full week without symptoms between the influenza and the pneumonia. In 2 cases (9 and 11) there was a temporary remission of fever and slight improvement after a few days of sulfadiazine (2-[paraaminobenzenesulfonamido]-pyrimidine) therapy.

The outstanding feature of all these cases was the persistent and intense dyspnea and cyanosis, which were only slightly affected by oxygen administration. The patients were irrational and stuporous most of the time. Signs of diffuse bronchitis and of scattered patches of consolidation were present throughout the lung but were usually more extensive in one or two lobes. Signs of extensive cavitation suggestive of advanced pulmonary tuberculosis were made out clinically and by

7. (*a*) MacCallum, W. G.: The Pathology of the Pneumonia in the United States Army Camps During the Winter of 1917-18, Monograph 10, Rockefeller Institute for Medical Research, 1919. (*b*) Goodpasture, E. W., and Burnett, F. L.: The Pathology of Pneumonia Accompanying Influenza, U. S. Nav. M. Bull. **13**: 177-197 (April) 1919. (*c*) Goodpasture, E. W.: The Significance of Certain Pulmonary Lesions in Relation to the Etiology of Influenza, Am. J. M. Sc. **158**: 863-870 (Dec.) 1919. (*d*) Wolbach, S. B.: Comments on the Pathology and Bacteriology of Fatal Influenza Cases Observed at Camp Devens, Massachusetts, Bull. Johns Hopkins Hosp. **30**:104-109 (April) 1919. (*e*) Winternitz, M. C.; Wason, I. M., and McNamara, F. P.: The Pathology of Influenza, New Haven, Conn., Yale University Press, 1920.

Case No.	Sex and Age, Yr.	Dates: Hospital Admission	Dates: Onset of Influenza	Dates: Onset of Pneumonia	Dates: Death	Bacteriologic Data: Sputum	Bacteriologic Data: Blood	Bacteriologic Data: Other Sources	Chemotherapy: Drug	Chemotherapy: Gm.	Comment on Clinical Course and Autopsy †
8	♀ 74	1/12	1/5	1/5	1/20	1/15, SA, Pn XVII, SV	.....	HB, 0; RL, SA; HI, SV	...	...	Irrational, severe cough; Paget's disease of skull, auricular fibrillation, B. P. 160/110; WBC 11,600, low grade fever, bilateral patchy consolidation, emphysema; 1/17 improved, sat up; 1/19 irrational, increasing dyspnea, stupor; autopsy: fibrinous pleuritis, pulmonary fibrosis, walled-off abscesses connected with dilated bronchi, mostly in lower lobes; arteriosclerotic heart disease, healed pyelonephritis, Paget's disease of skull and spine
9	♀ 76	1/24	?	1/18	2/9	1/24, SA	1/24, 0 1/27, 0	HB and LL, 0; RU, SA, few HI	SD	28	"Cold," then prostration and chest pain (poor history); WBC 24,000, dropped gradually to 5,500, then rose to 18,700; NPN 49, dropped to 30; patchy pneumonia RM and RU; extrasystoles; improvement under therapy, then low grade fever, increasing dyspnea, cyanosis and extension of pulmonary involvement; autopsy: bilateral fibrous pleuritis, firm gray fibrosis of lung parenchyma in RU and RM, moderated bronchiectasis, mostly in both lower lobes
10	♀ 50	12/30	12/24	12/24	2/18	1/2, SA, few Pn XIV; 1/7, SA, SV; 1/15, SA, SH; 1/28, SA, SH	2/7, SA, many others before and after, 0	HB, 0; LL and RL, SH and SA; abs. RL, SH and SA	ST	280	12/24 "grip," coryza, weakness, cough; 12/30 acute air hunger, bilateral bronchitis and patchy consolidation of lower lobes, irregular fever, marked and persistent dyspnea and cyanosis, WBC 9,000 to 18,000; autopsy: hypertrophy and dilatation of right auricle and ventricle, abscesses in myocardium, marked fibrosis, bronchiectasis and thick-walled abscesses in both lungs, few scattered abscesses in liver and spleen and kidneys (temperature chart and roentgenogram of chest shown in figs. 1 and 2)
11	♂ 81	1/26	? 1/5	? 1/5	2/3	1/29, SA, few SV	1/26, 0	RU, 0; RL and LL, SA, few SV	SD	42	Cough, vomiting (poor history); feeble; bronchopneumonia mainly in RL, fever and pulse rate dropped after SD begun, then rose again; WBC 10,000, rose to 27,000 on 1/28; increasing dyspnea and cyanosis; autopsy: bilateral organizing pneumonia and fibrous pleurisy
12	♂ 64	1/20	1/9	1/19	2/3	1/21, SA, SV	1/20, 0 1/21, 0	.....	SD	79	Improvement after "grip," then sudden dyspnea, cough, yellow bloody sputum; disorientation; diffuse patchy consolidation; WBC 17,000, dropped to 9,000 on 1/26 and rose gradually to 35,000; irregular temperature to 103 F.; abscess cavities in RU; temporary improvement on SD; thrombophlebitis of right leg 2/1; OFA > 1:128 on 2/2; no autopsy
13	♀ 56	1/7	1/5	1/5	3/1	1/9, SA, few SV, Pn III; neg. for TB 14 times	1/7, SA; many others, 0	.....	ST	72	Severe cough, substernal tightness while nursing son for "influenza"; fever, prostration, cyanosis, dyspnea, thick yellow sputum; diffuse patchy consolidation, extending to entire lung; many large abscess cavities revealed by roentgen examination; WBC 5,000 to 18,000; right ventricular predominance (cor pulmonale); died with symptoms of cardiac failure; no autopsy

* In addition to the abbreviations indicated in table 1, the following ones have been employed in tables 2 and 3: Pn, pneumococci, with the type represented by a Roman numeral; TB, tubercle bacilli; HI, Haemophilus influenzae; BP, blood pressure; and NPN, nonprotein nitrogen measured in milligrams per hundred cubic centimeters of blood.

† For more detailed autopsy observations in cases 8 through 11, see cases 5 through 8, respectively, in the paper by Wollenman and Finland.[3]

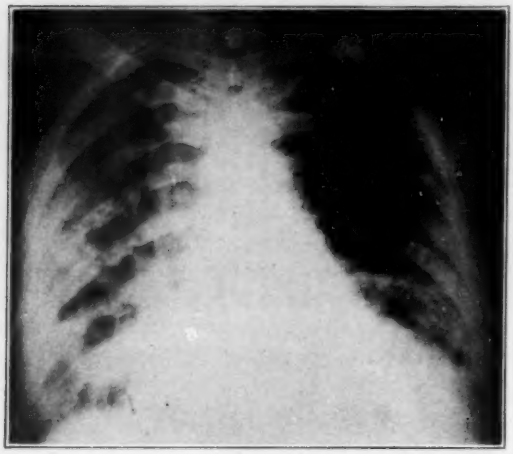

Fig. 1 (case 10).—Bedside roentgenogram of the chest made at the end of the sixth week of illness. Extensive bilateral fibrosis and cavitation (abscesses) are evident, especially in the lower lobes, and the heart is enlarged to the right. For the clinical chart in case 10 see figure 2.

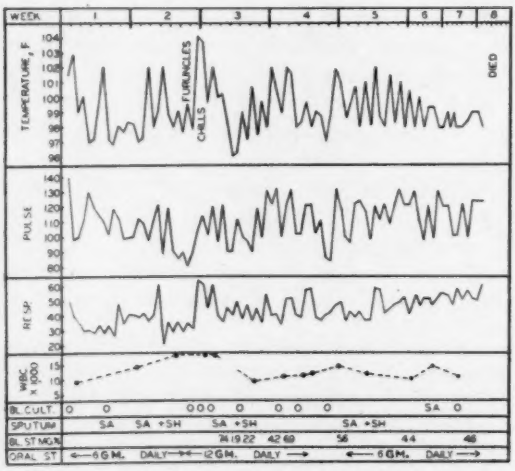

Fig. 2 (case 10).—Clinical chart for M. B., a 50 year old woman admitted to the hospital Dec. 30, 1940, six days after the onset of pneumonia. Under blood culture (*BL. CULT.*) *O* signifies the culture was negative for growth. For the other abbreviations see the starred footnote to table 1.

roentgen examination in case 13, but numerous examinations of the sputum failed to reveal tubercle bacilli. In the 2 cases of the longest illness there was evidence of increasing failure of the right side of the heart with marked distention of the cervical veins and engorgement of the liver. In case 10 hypertrophy of the right ventricle and dilatation of both chambers of the right side of the heart were noted at autopsy, and in case 13 enlargement of the right side of the heart was revealed by roentgen examination and the electrocardiogram showed right ventricular predominance.

Autopsies were performed in 4 of these cases,[8] and all revealed similar conditions in the lungs. The bronchi were dilated and filled with exudate, and their walls were necrotic and fibrosed. There were numerous thick-walled abscess cavities, some of which communicated with bronchi or bronchioles, and much of the intervening parenchyma was replaced by fibrous tissue. Some of the uninvolved parenchyma, especially in the upper lobes or at the periphery of the lungs, was emphysematous. The picture was similar, in general, to that of the organizing pneumonias described by Winternitz and associates [7e] and others among the influenzal pneumonias of 1918.

Cultures of sputum and of the lungs showed Staph. aureus predominating in every instance, but small numbers of pneumococci and Str. viridans were also obtained from sputum, and influenza bacilli were obtained from the lungs in 2 cases. In case 10 hemolytic streptococci appeared in the sputum and persisted; they were later found in the lungs. Blood cultures were positive for Staph. aureus on a single occasion in 2 cases; all others, including those made at autopsy, yielded no growth. In 1 of the cases with bacteremia (case 10) multiple miliary abscesses were encountered in the viscera at autopsy. Serologic studies were made in only 1 case in this group (case 12) and showed complement fixation with influenza A virus to a high titer (1 : 128) on the day before death, which was twenty-four days after the onset of clinical influenza. This may be presumed to be indicative of recent infection with influenza A virus.

SEVERE STAPHYLOCOCCIC PNEUMONIA WITH RECOVERY (TABLE 3 AND FIG. 3)

A third group comprises 11 cases in which the symptoms during the early stage of the pulmonary infection were somewhat like those in the fatal cases. The pneumonia in these cases was limited largely to one lobe or to one lung, and improvement gradually occurred under intensive therapy with derivatives of sulfanilamide. The patients in this group of cases were generally younger than those in the preceding groups; with 1 exception they were under 45, and 5 of them 25 or younger. Most of the patients also had diffuse tracheobronchitis.

TABLE 3.—*Summary of Clinical and Laboratory Data in Eleven Cases of Severe Staphylococcic Pneumonia Complicating Influenza with Recovery* *

Case No.	Sex and Age, Yr.	Dates: Hospital Admission	Dates: Onset of Influenza	Dates: Onset of Pneumonia	Dates: Symptomatic Improvement	Dates: Afebrile	Dates: Discharge	Bacteriologic Data: Sputum	Bacteriologic Data: Blood	Bacteriologic Data: Pleural Fluid	WBC Range During Fever	Lung Chiefly Involved, Roentgen Examination	Chemotherapy: Drug	Chemotherapy: Gm.	Comment on Clinical Course
14	♂ 16	12/27	12/20	12/24	1/5	2/13	2/21	12/28, SV (mouse); 1/1, SA	12/27, 28 and 29, 0; 1/1, SA; 1/6, 9 and 14, 0	12/29, 1/1 and 1/3, SA	15,000-20,000	RL, fluid	SD ST	35 112	Scarlatiniform eruption on admission; 250 cc. thin pus removed at each thoracentesis; catheter drainage and lavage with 0.5% NaST in saline 1/5; rib resection 1/13, thick-walled cavity almost empty; ST rash and fever; CFA negative on 12/28, 3/25
15	♂ 44	1/16	1/9	1/15	1/30	1/28	2/27	1/17, Pn IV (N)	1/16, 0	1/19, 20, 21 and 23, SA	27,000-13,000	RL, fluid	SD	44	Blood-stained white sputum, marked dyspnea, diffuse bronchitis; 80-800 cc. pus removed at each puncture; rib resection 1/23, gradual improvement
16†	♀ 25	1/22	1/3	1/4	3/17	3/17	3/25	1/8, SA; 1/22 and 23, SA, SV	1/22, 0	.....	15,000-23,000	RU, RM; cavities in RU	ST	70	Severe tracheobronchitis, followed by consolidation and large abscess; blood-stained sputum; drained by rib resection 1/23; ST in wound; secondary operation 2/19
17	♂ 37	1/14	1/10	1/13	1/29	2/7	3/12	1/15, SA, Pn XVIII; 1/17 and 25, SA; 2/3 and 12, SA, SV	1/15, 17 and 21, 0	1/16 and 18, SA; 1/20, no fluid	3,000-16,000	RL, fluid	ST SD	106 31	White, blood-streaked sputum; bronchitis and bronchopneumonia; thick, reddish purulent fluid, 200 cc. removed 1/16, 20 cc. 1/20, replaced by 0.5% NaST in saline; ST rash, 1/30 changed to SD; CFA >1:64 on 2/15 and 3/1
18	♂ 17	1/3	12/28	1/4	1/10	1/14	1/30	1/8, SV	1/6 and 20, 0	1/8, 12 and 13, SA	17,000-23,000	LL, fluid	SD ST	21 71	Signs of pneumonia followed by those of fluid; 20-180 cc. thick pus removed each time; cleared completely without operation; ST rash and episcleritis 1/18

19	♂ 14	1/3	12/31	12/31	1/10	1/10	2/1	1/6, Pn VI (N); 1/8 and 12, SA, SV; 1/11, SA	1/3, 6, 7, 9 and 11, 0	1/6, 9 and 15, SA; 1/20, no fluid	17,000-10,000	LL, fluid	SD	35	Three thoracenteses each yielded 5-10 cc. thick pus; no fluid fourth time; critical drop in temperature; no operation
20	♂ 64	1/19	1/12	1/16	2/6	2/11	3/16	1/20, 21 and 23, SA, few SV; 1/28 and 3/1, SA	1/19, 24, 26, 28, 29 and 30, 0	1/28, 29 and 2/7, 0	15,000-25,000	Right lung, fluid, ? cavities	SD ST SD	54 83 31	Rusty sputum; recurrent chills; marked prostration; small amounts thin, straw-colored pleural fluid; gradual improvement; signs in lung persisted for 4 mo.; ST rash and episcleritis 2/9-2/13; multiple transfusions; CFA 1:32 on 3/1 and 1:4 on 4/15
21	♂ 44	1/12	1/7	1/9	1/13	1/23	2/8	1/12, 15 and 25, SA, few SV	1/12 and 13, 0	1/23, 0	16,000-4,000	RL, RM, fluid, cavities	SD	100	Mild diabetes, readily controlled; marked dyspnea, prostration; brown sputum; rapid improvement after SD started; 10 cc. serous fluid obtained once; CFA 1:8 on 1/12 and 1:64 on 3/22
22	♂ 35	1/31	1/8	1/8	2/6	2/10	3/27	2/7, 10 and 3/4, SA, few SV; 2/9 and 3/6, SA, Pn XVIII	1/31, SA; 2/6, 14 and 18, 0	.....	11,000-19,000	RL, ? cavities; signs of TB in RU	ST	59	Six weeks' cough before "flu"; RL consolidation cleared, signs in LU persisted; sputum neg. for TB; guinea pig inoculated with gastric washing 3/28, pos. for TB; fever 2/21-3/4; ST rash 2/9; CFA 1:64 on 3/22 and 1:16 on 4/28 (fig. 3)
23	♂ 21	1/10	1/7	1/7	1/19	1/27	2/5	1/10, 11, 12 and 17, SA, few SV; 1/28, SA, SH	1/10, 11, 13, 18, 19 and 20, 0	.....	6,000-16,000	RL, ? fluid or thick pleura	ST SD	25 40	Tracheobronchitis on admission, then consolidation RL and ? fluid; jaundice on 1/13; II, 30
24	♂ 38	1/22	1/1	1/10	1/24	2/11	2/18	1/22, SV, HI; 1/25, 28 and 30, SA, SV	1/22, 25, 26 and 28, 0	1/28 and 31, 0	10,000-17,000	LL, fluid, cavities	SD ST	48 25	Marked improvement after chemotherapy; fever continued, copious brown sputum; 15 cc. thin pleural fluid twice; lung cleared completely

* In addition to the abbreviations indicated in tables 1 and 2, the following ones have been employed in table 3: (N), direct typing of pneumococci by Neufeld capsule swelling; II, icterus index; NaST, sodium sulfathiazole.

† The patient in this case was treated in other hospitals. Dr. Joseph M. Rosenthal permitted us to report the data.

Pleural fluid varying in amount from 10 to 800 cc. was obtained by thoracentesis in 8 cases. The fluid in 3 cases was sterile every time, while in each of the remaining 5 cases an abundant growth of Staph. aureus was obtained from the fluid on two or more occasions. In 2 of the latter cases treatment was by rib resection; in the other 3 the condition cleared completely and did not require surgical intervention. In 1 case large abscess cavities in the upper lobe of the right lung were drained through a rib resection and later required a secondary operation

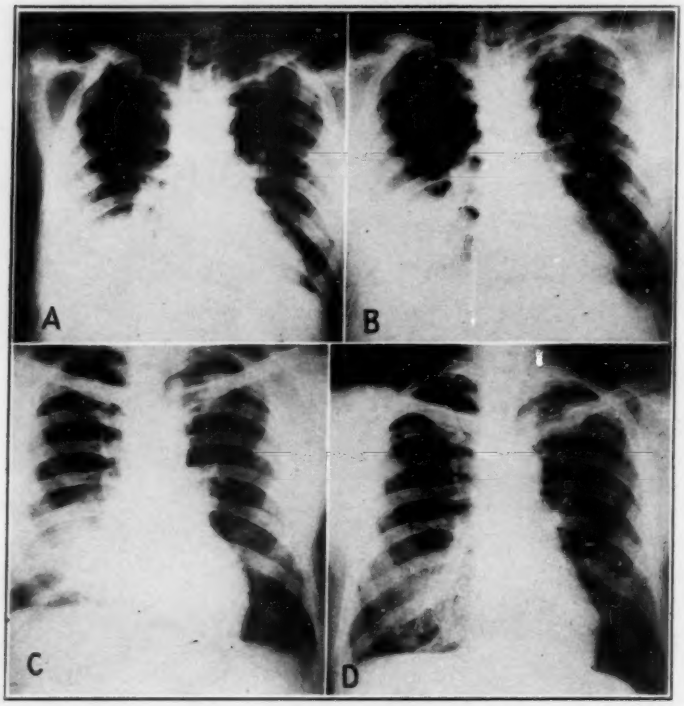

Fig. 3 (case 22).—Serial roentgenograms of the chest, showing essential clearing of the acute process in the right lung and pleura and persistence of the tuberculous infiltration near the apex of the left lung. The roentgenograms were made on (*A*) Feb. 11, 1941; (*B*) February 27; (*C*) March 12, and (*D*) April 17.

to evacuate an undrained area of suppuration. In at least 2, and probably 4, of the other cases, the patients had areas of abscess formation within the affected lung which were discernible as rarefied areas by roentgen examination. They apparently healed completely, presumably after draining into bronchi, as evidenced by profuse purulent sputum.

The results of culture of sputum in these cases were similar to those in the fatal cases. In each of 2 cases, including 1 in which the patient had infected pleural fluid, a blood culture positive for Staph. aureus was obtained on one of several occasions. Complement fixation tests with influenza viruses were done with the serums of 5 patients in this group. In 4 cases the serum showed significantly high titer or more than a fourfold change of titer with influenza A virus. In the fifth case (14) serum examined on the eighth day after the onset of influenza and again three months later gave negative results.

Recovery in these cases was slow, but eventually it was complete as far as could be ascertained. In some of these cases the patients have now been followed up for more than a year and have remained well. Only 2 of the patients became afebrile within ten days of the onset of pneumonia, while in the others fever and other evidences of active infection persisted for two to five weeks. In case 20 roentgenographic signs of fluid persisted for over four months and eventually cleared, leaving evidence of residual pleural thickening and adhesions. One patient (case 22, fig. 3) had a history of cough for six weeks prior to the onset of influenza. In this patient, although the pneumonic consolidation was limited chiefly to the lower lobe of the right lung, where there was also evidence of abscess formation, crepitant rales were heard in the upper lobe of the left lung throughout his stay in the hospital, and there was persistent mottled infiltration in this region in the roentgenograms. The signs in the lower lobe of the right lung cleared slowly and apparently completely, while those in the apical region of the left lung remained unchanged. Sputum smears were negative for tubercle bacilli during the acute illness. No sputum was obtainable later, but material aspirated from the stomach yielded tubercle bacilli on guinea pig inoculation.

ACUTE STAPHYLOCOCCIC PNEUMONIA WITH RAPID AND COMPLETE RECOVERY

In the fourth group there were 18 cases, in all of which the patients had symptoms and signs (including roentgenographic evidence) of pneumonia which began between December 30 and January 20, at the same time as or a few days after an attack of clinical influenza. In 13 cases the patients were less than 45 years old, and in 3 they were over 70. Staph. aureus predominated in cultures of sputum in every case; Str. viridans occurred in most of the cases, and pneumococci of higher types and influenza bacilli were found together in 1 case and separately in others. Blood cultures were positive for Staph. aureus in 2 cases and showed no growth in all the others. A sterile pleural effusion was demonstrated in 1 case (33). The serum in this case showed complement-fixing antibodies for influenza A in a significant titer.

The maximum temperature in different cases varied from 101 to 105 F., and the pulse rate, from 100 to 140 per minute; respirations were somewhat rapid, and the leukocyte count at the height of the fever varied between 4,000 and 31,000. Pulmonary consolidation was limited chiefly to one lobe in 10 cases and to two lobes in the others; it appeared by physical signs and roentgen examination to be uniformly distributed throughout most of the involved lobes in 5 cases and as irregular patches in the others. One of the patients, a Negress, had a rash which she thought was "measles" at the beginning of her pneumonia, but this had cleared without residual signs at the time of admission to the hospital.

TABLE 4.—*Summary of Some of the Relevant Data in Sixty-Six Cases of Staphylococcic Infection of the Lungs Complicating Clinical Influenza* *

Group †	I	II	III	IV	V	VI(a)	VI(b)	VI(c)	Total
Number of cases	7 (7)	6 (6)	11	18	4	7 (6)	3	10 (2)	66 (21)
Age, years									
14-39	1 (1)	..	8	9	3	..	3	5	29 (1)
40-59	5 (5)	2 (2)	2	6	1	2 (1)	..	2	20 (8)
60 and over	1 (1)	4 (4)	1	3	..	5 (5)	..	3 (2)	17 (12)
Positive blood culture									
Staph. aureus	1 (1)	2 (2)	2	2	..	1 (1)	3	0	11 (4)
Other organisms	1 (1)	..	..	..	..	..	..	4	5 (1)
Pleural fluid									
Sterile	..	..	3	1	..	..	1	1	6
Infected (with staphylococci)	3 (3)	..	5	..	..	..	..	1	9 (3)
Chemotherapy									
Sulfathiazole	3 (3)	2 (2)	2	5	2	3 (3)	1	3	21 (8)
Sulfadiazine	2 (2)	3 (3)	3	11	1	..	1	6 (2)	27 (7)
Sulfathiazole and sulfadiazine	1 (1)	..	6	..	..	..	1	1	9 (1)
Sulfapyridine	1 (1)	..	..	1	..	1 (1)	..	..	3 (2)
None	..	1 (1)	..	1	1	3 (2)	..	..	6 (3)

* The figures in parentheses represent the number of cases of fatal infection included.

† Roman numerals have been used to designate the following groups: I, fatal acute and fulminating pneumonia; II, fatal organizing pneumonia; III, severe pneumonia, extensive or with complications; IV, acute pneumonia with rapid recovery; V, influenza with tracheobronchitis (most of the cases in this group were excluded for lack of bacteriologic data); VI (a), staphylococcic infection of the lungs complicating cardiac disease or other pulmonary disease; VI (b), focal infection, and VI (c), staphylococcic superinfection of pneumococcic lobar pneumonia.

In all but 1 of these 18 cases the patients were treated with the usual doses of three derivatives of sulfanilamide from the time they entered the hospital. All, including the 1 who did not receive chemotherapy, were markedly improved within eighteen to forty-eight hours, and all but 2 were completely afebrile within one to four days after admission.

INFLUENZA AND TRACHEOBRONCHITIS

The four groups of cases already described include all those with definite pulmonary consolidation following an attack of clinical influenza in which the Staphylococcus was the only or the predominant organism and was considered to be related to the pulmonary lesion. A fifth and

large group of cases was encountered in which symptoms of influenza were associated with or followed by increased prostration, hoarseness and severe cough accompanied by presternal soreness and production of tenacious, purulent and occasionally blood-streaked sputum. The temperature in these cases was usually high (102 to 104 F.), the pulse rapid (100 to 140 per minute) and the respiratory rate somewhat increased. The leukocyte count was within the normal range (6,000 to 10,000). The only abnormal physical signs elicited in the lungs were numerous musical and occasional fine crepitant rales scattered throughout the lungs; the latter were heard most frequently at the bases. Roentgenograms of the chest were usually read as normal, but close inspection often revealed increased bronchial markings and some areas of fine mottling, especially in the lower lobes. Fever and prostration in these cases lasted five to ten days, with a brief remission in some cases, but the cough and sputum persisted for several days longer. The course seemed to be affected only slightly, if at all, by therapy with either sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) or sulfadiazine.

This clinical picture was probably the predominant one in the cases of severe influenza which were presumed to be uncomplicated. It corresponded in most respects to the influenza with "bronchiolitis" which Stuart-Harris and his co-workers [8] considered to be the commonest lesion encountered in the influenza epidemic of 1936-1937 in England and which was also described at the same time by Scadding.[9] Blood cultures failed to yield growth in any case. Other bacteriologic studies were carried out in only a few of these cases, and they indicated that the flora in the sputum consisted chiefly of common mouth organisms. In 16 cases that were studied the only or the predominant organisms were alpha hemolytic streptococci in 7 cases, beta hemolytic streptococci in 3, pneumococci (types XIII and XIX) in 2 and Staph. aureus in 4. In the last-named 4 cases the patients were young or middle-aged women whose illnesses did not differ in most respects from those caused by the other organisms except that the fever and symptoms persisted somewhat longer and seemed to respond less readily to therapy with a derivative of sulfanilamide. Whether the Staphylococcus played any role in the pathologic condition in the lungs in these 4 cases is, of course, open to question.

Serologic studies were made in 1 of the 4 cases in which staphylococci were isolated, and a significant titer of complement fixation with influenza A virus was demonstrated. In 2 other cases in which the

8. Stuart-Harris, C. H.; Andrewes, C. H., and Smith, W.: A Study of Epidemic Influenza, with Special Reference to the 1936-7 Epidemic, Medical Research Council, Special Report Series, no. 228, London, His Majesty's Stationery Office, 1938.

9. Scadding, J. G.: Lung Changes in Influenza, Quart. J. Med. **6**:425-465 (Oct.) 1937.

clinical course was similar the virus itself was isolated by ferret inoculation of nasopharyngeal washings obtained in the early febrile stage.[2e] Staphylococci were not obtained in these 2 cases, and the course of illness in them was brief and comparatively mild.

MISCELLANEOUS CASES OF STAPHYLOCOCCIC PNEUMONIA

There were a variety of other cases of staphylococcic infections of the lung which were encountered during the same period. In the majority of these cases an antecedent history of influenza-like symptoms could be elicited. Some of the important features of these cases may be summarized briefly.

In 5 cases the patients, all over 70 years of age, had chronic cardiac disease, and in 1 case a man aged 50 had chronic bronchial asthma; all of them were admitted to the hospital between January 10 and 27 for an acute exacerbation of their chronic illness associated with an acute infection of the respiratory tract. They all died within ten days and were found to have diffuse bronchopneumonia and congestive cardiac failure at autopsy. The asthmatic patient also had severe bronchiectasis and cor pulmonale. Abundant growth of Staph. aureus was obtained from the lungs in each case. This was the only organism recovered in 2 cases, while in the others small numbers of alpha and beta hemolytic streptococci, pneumococci (type XXIX) and Escherichia coli were obtained in addition. Culture of heart blood yielded the staphylococcus in 1 instance, but showed no growth in the others. Cultures of sputum were made only in the case of the asthmatic patient and yielded Staph. aureus in almost pure culture from several specimens.

In a seventh case a man of 55 was admitted to the hospital during the same period with symptoms of acute pneumonia following typical influenza. There were signs of irregular consolidation limited mostly to the upper lobes, and staphylococci predominated in cultures of several specimens of purulent sputum. Stained smears of the last three of eight specimens examined, however, also showed acid-fast bacilli. The patient's fever and acute respiratory distress subsided after a week, but the lesion in the upper lobes persisted and later had the characteristic roentgen appearance of tuberculous infiltration.

Three cases of focal infections are also of interest. In 1 case the patient was a woman of 31 who four weeks post partum had a breast abscess incised (culture not done); then clinical influenza developed, which was followed in a week by pneumonia of the lower lobe of the right lung. This was complicated, in turn, by a sterile pleural effusion. Cultures of thick purulent sputum on several occasions yielded Staph. aureus in almost pure culture, and this organism was also grown from

one of three blood cultures. The patient improved and became afebrile after three days of sulfadiazine treatment, and the lung gradually cleared after showing small areas suggestive of cavities in a roentgenogram. The patient in the second case was a Negress aged 34 who had been in the hospital for several weeks and had recovered successively from exfoliative dermatitis (due to arsphenamine) and sepsis caused by hemolytic streptococci. In the latter part of December symptoms of influenza and pneumonia developed; Staph. aureus was recovered in several blood cultures and was predominant in cultures of the sputum, which also contained some hemolytic streptococci. The patient recovered from this illness after a long and severe course with intensive sulfathiazole and sulfadiazine therapy. In the third case typical influenza developed in a youth of 19 on January 12; he had fever (a temperature up to 104 F.) for five days, after which he improved. On January 22 he had a chill, cough, headache and stuffiness of the nose. When seen two days later he had severe maxillary sinusitis and scattered rales in the lungs. Sputum and nasal secretions yielded Staph. aureus in pure culture, and the same organism was obtained from the blood culture. Sulfathiazole therapy was given; drainage of the sinus was established, and the patient made a rapid and uneventful recovery.

OBSERVATIONS ON PNEUMOCOCCIC PNEUMONIA IN RELATION TO THE INFLUENZA AND THE STAPHYLOCOCCIC INFECTIONS

A few observations concerning some of the cases of typical lobar pneumonia encountered during the influenza epidemic are worth mentioning, since they are relevant to the subject at hand.

During the first three weeks of January 22 patients admitted to four different medical wards with typical lobar pneumonia associated with the common types of pneumococci gave a history of symptoms of influenza beginning one to ten days before the onset of the pneumonia. In 10 of the 22 patients cultures of sputum showed Staph. aureus in abundance, either together with pneumococci from the start or appearing in later specimens at a time when the pneumococci declined in number or could no longer be isolated. Two of these 10 patients died; both had type IV pneumococci and staphylococci in their sputum, and cultures made from the lung of 1 of these patients at autopsy showed both organisms. The other 8 patients had a prolonged course with low grade fever, and empyema developed in 1. The lesions in the lungs and the empyema cleared slowly but completely, although in some there was suggestive roentgen evidence of small cavities in the affected lobes during the course of the disease. Three of these patients had type I, 1 had type VIII and 4 had type III pneumococci in the sputum. One of the patients with

type I and 3 with type III organisms had blood cultures positive for pneumococci, but the pleural fluid obtained from the patient with pneumonia caused by type VIII pneumococci yielded a pure culture of Staph. aureus.

While cases of "superinfection" with other organisms in the course of pneumococcic pneumonia are not infrequent,[10] the Staphylococcus is not often the cause of such secondary infections. It is found much less frequently than hemolytic streptococci under such circumstances. The high proportion of cases with staphylococci in this brief interval is therefore of added interest. Furthermore, similar cases were noted even before the appearance of influenza, since 3 instances had been recognized in the latter part of November. It is also worth mentioning that only 4 cases of pneumonia caused by hemolytic streptococci were encountered during this epidemic. In 2 blood cultures were positive for such organisms; and in 1 there was associated empyema. In all four cases recovery followed sulfadiazine treatment.

Other indirect evidence of infection with influenza A virus in cases of typical pneumococcic pneumonia was obtained from the serologic studies of Pearson and his co-workers.[20] They carried out complement fixation tests with influenza viruses on the serums obtained in a number of cases of classic lobar pneumonia due to common types of pneumococci and found titers of influenza A antibodies which were significantly high or which showed sufficient change to suggest recent infection with this virus. There was no evidence of infection with influenza B virus. The serums were originally collected for the purpose of studying the development of pneumococcus antibodies in cases of pneumonia in which treatment was with sulfathiazole and sulfadiazine. Type-specific pneumococcus antibodies were demonstrated during convalescence in almost all of these cases.[11] Of the patients admitted to this hospital during January, virus studies were made on 16, and the results suggested influenza A infection in 11, or 69 per cent. In the preceding and succeeding months the percentage of such positive results was considerably smaller.

SUMMARY AND COMMENT

We have presented the important features of 66 cases of staphylococcic infection of the lungs complicating clinical influenza in adults. In all cases the onset of symptoms of influenza occurred during the period of four weeks when the epidemic was prevalent in and around Boston.

10. Finland, M.: The Significance of Mixed Infections in Pneumococcic Pneumonia, J. A. M. A. **103**:1681-1686 (Dec. 1) 1934.

11. Finland, M.; Strauss, E., and Peterson, O. L.: Antibody Response of Patients with Pneumococcic Pneumonia Treated with Sulfadiazine and Sulfathiazole, Ann. Int. Med. **16**:1-16 (Jan.) 1942.

Taken together, these cases offer a sort of panorama of the variety of forms in which the Staphylococcus manifested itself in the respiratory tract of patients with influenza during this outbreak.

Some of the more relevant data are summarized in table 4. All age groups were represented. Cases of such infection occurring in infants and children were not included, but a number of such patients with pneumonia having bacteremia and empyema caused by Staph. aureus were treated in the hospital during this period, and some of the infants died. Among the 66 adults the deaths occurred predominantly in patients over 60 years old, but the fatalities in the acute fulminating infections occurred mostly in middle-aged people. There were 21 deaths in all, a mortality of 32 per cent. Actually, the mortality probably was lower, since many more cases of influenza with minimal signs in the lung (group V) might have been included had more complete bacteriologic studies been made in all such cases.

Blood cultures positive for Staph. aureus were obtained in 11 cases, in 4 of which the patients died. Hemolytic streptococci were obtained from the blood in 1 case of fulminating disease, and pneumococcic bacteremia was demonstrated in 4 cases of lobar pneumonia in which there were mixed infections or a superinfection with staphylococci. Pleural effusions were encountered in 15 cases. These proved to be sterile in 6 cases, while cultures of pleural fluid in the other 9 yielded Staph. aureus. In 2 of the 9 cases the fluid was discovered at autopsy.

The virus studies carried out by Pearson and his associates [2e] indicated that influenza A played a role in this epidemic and in these cases. The virus was isolated in 2 cases of uncomplicated influenza and was presumptively demonstrated in the lung in 1 of the acute and fatal cases. Immunologic evidence of infection with influenza A (and not influenza B) was obtained in 7 cases and was also demonstrated in 3 of the 5 cases of staphylococcic pneumonia that were encountered during this epidemic at the Peter Bent Brigham Hospital.[4] There was evidence of influenza A infection in cases of pneumococcic pneumonia encountered here during the height of the epidemic, and the virus was isolated in cases of influenza in many other parts of the country.[2]

Therapy with one or more derivatives of sulfanilamide was used in all but 6 cases. In some of the cases of severe disease 9 and even 12 Gm. was given daily for several days, but in most cases the patients received the usual dose of 1 Gm. every four hours during most of the febrile stage and either 6 or 4 Gm. daily for a few days thereafter. Sulfathiazole and sulfadiazine seemed to be equally effective. Some patients were changed from one of these drugs to the other, either because the supply of sulfadiazine was temporarily exhausted or because of toxic effects

from sulfathiazole. Treatment in the cases of severe disease was continued for one to four weeks, but in cases of the milder forms the drugs were given for only two to five days. It is of particular interest that in 4 of the 6 cases of empyema (excluding the 3 cases of fulminating disease, in 2 of which the infected fluid was found at autopsy) complete recovery under chemotherapy occurred after one or more thoracenteses and did not require surgical drainage, although thick purulent fluid was obtained in some cases. The occurrence of sterile pleural effusions in cases of severe infection with recovery and the low fatality in cases with positive blood cultures are further indications of the efficacy of the drugs in the treatment of these infections.

While in 1 case of large pulmonary abscesses treatment was surgical, in others less extensive cavitation apparently healed completely without operation. Cases in which large abscesses associated with staphylococcic pneumonia healed spontaneously have been observed by one of us (M. F.) and have also been reported by Reimann.[12] Under such circumstances there is usually profuse purulent expectoration at the time when the fever begins to subside.

The exact role of the Staphyloccocus in all of these cases is difficult to evaluate. The high incidence of abscesses of the lung, of empyema and of bacteremia associated with pure cultures of Staphylococcus is strong evidence that this organism must have played an important role in the pulmonary infections described.

Staphylococcic pneumonia has been recognized since the influenza pandemic of 1889-1890. The distinctive pathologic changes were noted by Fraenkel in cases of influenzal pneumonia and later were identified with the staphylococcic bronchopneumonias by him[13] and by Netter.[14]

In that epidemic, while the Staphylococcus was cultured from the lungs occasionally, it was not frequent and was not considered important. The influenza bacillus was considered by most workers to be the significant organism,[15] although the Streptococcus was thought by some, notably Finkler,[16] to be the important cause of the severe influenzal pneumonias.

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12. Reimann, H. A.: Primary Staphylococcic Pneumonia, J. A. M. A. **101**: 514-520 (Aug. 12) 1933.

13. Fraenkel, A.: Spezielle Pathologie und Therapie der Lungenkrankheiten, Berlin, Urban & Schwarzenberg, 1904.

14. Netter: Etude bactériologique de la bronchopneumonie chez l'adulte et chez l'enfant, Arch. de méd. expér. et d'anat. path. **4**:28-65, 1892.

15. Leichtenstern, O.: Influenza, in Nothnagel, H.: Specielle Pathologie und Therapie, Vienna, Alfred Hölder, 1896, vol. 4, pt. 1, pp. 1-195.

16. Finkler, D.: Influenzapneumonie, Deutsche med. Wchnschr. **16**:84-86 (Jan. 30) 1890.

In the 1918 pandemic, also, while the influenza bacillus of Pfeiffer was found to be predominant in the lungs in fatal cases by many observers in some areas,[17] it was not frequent in others.[18] The hemolytic Streptococcus was apparently the most important organism found during that epidemic in the influenzal pneumonias that occurred in many localities, particularly in the United States Army camps.[19] Nevertheless, there were three reports during the 1918 epidemic of sizable groups of cases of influenzal pneumonia in which the Staphylococcus was the only or the predominant organism in a large proportion of the severe and fatal infections. All cases were encountered in military hospitals; the largest series, at Camp Jackson, S. C., was reported by Chickering and Park [20] and the others occurred at Malta [21] and in the Third Canadian General Hospital in France.[22] Since that time, individual cases or small groups

17. (*a*) Report on the Pandemic of Influenza, 1918-19, Ministry of Health, Reports on Public Health and Medical Subjects, no. 4, London, His Majesty's Stationery Office, 1920. (*b*) Fildes, P.; Baker, S. L., and Thompson, W. R.: Provisional Notes on the Pathology of the Present Epidemic, Lancet **2**:697-700 (Nov. 23) 1918. (*c*) MacCallum, W. G.: Pathology of the Pneumonia Following Influenza, J. A. M. A. **72**:720-723 (March 8) 1919. (*d*) Hall, J. N.; Stone, M. C., and Simpson, J. C.: The Epidemic of Pneumonia Following Influenza at Camp Logan, Texas, ibid. **71**:1986-1987 (Dec. 14) 1918. (*e*) Goodpasture and Burnett.[7b]

18. (*a*) Hirsch, E. F., and McKinney, M.: Epidemic of Bronchopneumonia at Camp Grant, Illinois: Preliminary Bacteriologic Report, J. A. M. A. **71**:1735-1736 (Nov. 23) 1918; (*b*) An Epidemic of Pneumococcus Bronchopneumonia, J. Infect. Dis. **24**:594-617 (June) 1919. (*c*) MacCallum.[17c]

19. (*a*) Arnold, L.: Classification of Streptococcus: II. Streptococci Isolated from Influenza Throats, Classified by Sugar Fermentations, J. Lab. & Clin. Med. **5**:591-592 (June) 1920. (*b*) Opie, E. L.; Blake, F. G.; Small, J. C., and Rivers, T. M.: Epidemic Respiratory Disease: The Pneumonias and Other Infections of the Respiratory Tract Accompanying Influenza and Measles, St. Louis, C. V. Mosby Company, 1921. (*c*) Opie, E. L.; Freeman, A. W.; Blake, F. W.; Small, J. C., and Rivers, T. M.: Pneumonia Following Influenza (at Camp Pike, Ark.), J. A. M. A. **72**:556-565 (Feb. 22) 1919. (*d*) Small, A. A.: Pneumonia at a Base Hospital: Observations in One Thousand and One Hundred Cases at Camp Pike, Ark., ibid. **71**:700-702 (Aug. 31) 1918. (*e*) Miller, J. L., and Lusk, F. B.: Epidemic of Streptococcus Pneumonia and Empyema at Camp Dodge, Iowa, ibid. **71**:702-703 (Aug. 31) 1918. (*f*) Dwinell, W. G.: Laboratory Reports on Epidemic Pneumonia, Camp Dodge, Iowa, Am. J. M. Sc. **158**:216-232 (Aug.) 1919.

20. Chickering, H. T., and Park, J. H., Jr.: Staphylococcus Aureus Pneumonia, J. A. M. A. **72**:617-626 (March 1) 1919.

21. Patrick, A.: Note on Staphylococcus Aureus Septicemia as a Complication of Influenza in an Epidemic in Malta, Lancet **1**:137-138 (Jan. 25) 1919.

22. Tytler, W. H.; Janes, R. M., and Dobbin, G. M.: Pathological and Bacteriological Findings in Fatal Cases of Pneumonia During the Influenza Epidemic of October and November 1918, in Studies of Influenza in Hospitals of the British Armies in France, 1918, Medical Research Committee, Special Report Series. no. 36, London, His Majesty's Stationery Office, 1919, pp. 77-87.

of cases of staphylococcic pneumonia have been reported in which there was an antecedent history of influenza-like symptoms or which occurred during influenza outbreaks.[23] Influenza A virus was isolated, along with Staph. aureus, from the lungs in 3 cases of acute fulminating pneumonia during the 1936-1937 epidemic in England by Stuart-Harris and his co-workers.[8] They suggested that when Staph. aureus is the secondary invader, death is apt to occur more quickly at a time when the virus is still easy to recover. One of these cases was also reported by Scadding.[9] Stokes and Wolman [23a] also reported isolation of influenza A virus and Staph. aureus in a single case in 1940.

It seems clear that the Staphylococcus may find fertile soil in the bronchi and lungs of occasional patients with influenza. Under certain conditions this organism may assume an epidemic spread along with the causative virus of influenza. Whether such a spread requires an unusual local prevalence of the organism or some peculiarity in the pathogenicity of the strains of Staphylococcus is not clear. In the case of the hemolytic Streptococcus the experience in the United States Army camps in 1918 suggested that the preceding history of infections in any given area may play an important role in the high incidence of that organism in the influenzal pneumonias. In many of these camps the epidemic of influenza was preceded by outbreaks of scarlet fever and measles, and these, in turn, were associated with a widespread prevalence of hemolytic streptococci.[24] In the present instance staphylococcic pulmonary infections had been noted prior to the epidemic in more than the expected frequency and have been encountered relatively often in the ensuing months.

From a practical point of view, it would seem important to bear in mind the possibility that both staphylococci and hemolytic streptococci may be associated with severe pulmonary complications of epidemic influenza. The results of treatment with sulfathiazole and sulfadiazine in the cases reported here indicate that, except perhaps in some of the

23. (*a*) Stokes, J., and Wolman, I. J.: The Probable Synergism of Human Influenza Virus and Staphylococcus Aureus in a Rapidly Fatal Respiratory Infection, Internat. Clin. **1**:115-122 (March) 1940. (*b*) Burgess, A. M., and Gormley, C. F.: Pneumonia in Relation to an Epidemic of "Mild" Influenza, with Report of Three Fulminating Cases Apparently Due to Staphylococcus Aureus, New England J. Med. **202**:261-264 (Feb. 6) 1930. (*c*) Stuart-Harris, Andrewes and Smith.[8] (*d*) Scadding.[9] (*e*) Reimann.[12]

24. (*a*) Opie, E. L.; Freeman, A. W.; Blake, F. G.; Small, J. C., and Rivers, T. M.: Pneumonia at Camp Funston: Report to the Surgeon-General, J. A. M. A. **72**:108-116 (Jan. 11) 1919. (*b*) Clendening, L.: Reinfection with Streptococcus Hemolyticus in Lobar Pneumonia, Measles and Scarlet Fever and Its Prevention, Am. J. M. Sc. **156**:575 (Oct.) 1918. (*c*) Cole, R., and MacCallum, W. G.: Pneumonia at a Base Hospital, J. A. M. A. **70**:1146-1156 (April 20) 1918. (*d*) Goodpasture and Burnett.[7b] (*e*) Small.[19d]

severe and fulminating forms, considerable benefit may be expected from their early and intensive use. Both these drugs seemed equally effective, but sulfadiazine has proved to be considerably less toxic.[25] It would also seem wise, during periods of epidemic prevalence of influenza, to employ these drugs in treatment in all cases of severe influenza, particularly if cultures of sputum show that hemolytic streptococci or Staph. aureus are unusually prevalent in an individual patient or in a community. This procedure was adopted here and elsewhere [26] and may have resulted in reducing the number and severity of pulmonary complications, although that fact is difficult to establish from the available data. In cases in which the pulmonary complications have not become established, a short course of treatment lasting two or three days should suffice.

CONCLUSIONS

Pneumonia caused by Staph. aureus may occur in patients with clinical influenza and may assume epidemic proportions in local areas during an influenza epidemic. The staphylococcic infection in the lung in an individual patient may assume any of a large variety of forms, varying from simple tracheobronchitis with minimal pulmonary involvement to a fulminating acute and fatal hemorrhagic and edematous pneumonia or a chronic organizing pneumonia with bronchiectasis and multiple abscesses. Intensive treatment of such infection with sulfadiazine or sulfathiazole is indicated. A brief course of treatment with these drugs is suggested for severe uncomplicated influenza in patients who harbor large numbers of pathogenic staphylococci or hemolytic streptococci or when these organisms are known to be prevalent in a community.

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25. Finland, M.; Strauss, E., and Peterson, O. L.: Sulfadiazine: Therapeutic Evaluation and Toxic Effects on Four Hundred and Forty-Six Patients, J. A. M. A. **116**:2641-2643 (June 14) 1941.

26. (*a*) Menefee, E. E., Jr., and Speed, J. A.: Treatment of Infections of the Respiratory Tract with Sulfonamides, North Carolina M. J. **2**:611-613 (Nov.) 1941. (*b*) Adamson, J. D., and Flett, R. O.: The Inefficacy of Sulfapyridine in Influenza, Canad. M. A. J. **46**:121-123 (Feb.) 1942.

EXOPHTHALMOS IN PATIENTS WITH VARIOUS TYPES OF GOITER

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Exophthalmos may be defined as protrusion of the globe of the eye. It occurs in diseases of the thyroid, sinusitis, intracranial arteriovenous aneurysms, benign or malignant tumors (either primary or metastatic) of the orbit or within the cranial vault, thrombosis of the cavernous sinus, myopia, xanthomatosis, congenital malformations of the skull, Paget's disease and other diseases of the bones and hypertension. It rarely appears as "voluntary" exophthalmos. The discussion in this paper will be limited to the exophthalmos that occurs in certain types of disease of the thyroid.

The mechanism of the exophthalmos associated with spontaneous or experimental thyrotoxicosis varies because of the anatomic peculiarities of different species of animals. In animals other than man stimulation of the cervical sympathetic nerves causes protrusion of the eyeball by contraction of Müller's muscle.[1] Although in man Müller's muscle is vestigial, many studies have been made concerning the role of cervical sympathetic stimulation in the exophthalmos of hyperthyroidism in human beings. Jonnesco [2] reported relief of exophthalmos in patients with toxic goiter following resection of the cervical sympathetic ganglions. Similar results were reported by Reinhard [3] but MacCallum and Cornell [1c] were unable to confirm this work. None of these investi-

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Statistical assistance was given by Dr. Nathan W. Shock, of the Department of Physiology and the Institute of Child Welfare, University of California, Berkeley.

1. (*a*) Müller, H., cited by MacCallum and Cornell.[1c] (*b*) Wagner, R.: Notiz über einige Versuche am Halstheile des sympathischen Nerven bei einer Enthaupteten, Ztschr. f. rat. Med. **5**:331-333, 1859. (*c*) MacCallum, W. G., and Cornell, W. B.: On the Mechanism of Enophthalmos, Tr. A. Am. Physicians **19**:56-63, 1904. (*d*) Karplus, J. P., and Kreidl, A.: Gehirn und Sympathicus: I. Zwischenhirnbasis und Halssympathicus, Arch. f. d. ges. Physiol. **129**:138-144, 1909.

2. Jonnesco, T.: The Enduring Results of Total Bilateral Resection of the Cervical Sympathetic in Basedow's Disease, Internat. Clin. **1**:136-148, 1903.

3. Reinhard, W.: Experimentelle Untersuchungen über die Beziehungen des Halssympathicus zur Schilddrüse, Deutsche Ztschr. f. Chir. **180**:170-176, 1923; Die Sympathicus-Ganglion Exstirpation bei Morbus Basedowii, ibid. **180**:177-197, 1923.

gators checked his clinical observations by measuring the degree of exophthalmos. It remained for Unverricht,[4] Mutch[5] and Pochin[6] to demonstrate in precise fashion that in human beings ocular proptosis was not produced by stimulation of the cervical sympathetic nerves.

The cause of the exophthalmos frequently associated with spontaneous hyperthyroidism in human beings has been a subject of much debate and speculation. An increase in retrobulbar fat has been postulated (see the references cited by Naffziger and Jones[7]). Some authors have expressed the belief that venous congestion and edema were responsible for the proptosis. Daniel[8] suggested that in patients with hyperthyroidism excessive tone of the rectus muscles could cause formation of local tissue fluids at the rate of 2 cc. per minute per hundred grams of muscle and thus could increase the pressure in the ophthalmic veins and produce edema. In connection with this hypothesis it is interesting to note Burch's[9] observation that the distensibility of the skin about the eyelids is much greater than that of skin of other parts of the body. In other words, increased hydrostatic pressure may have more profound effects on the orbital tissues than on tissues elsewhere in the body.

In recent years important pathologic changes in the extraocular muscles and in other orbital tissues have been demonstrated in cases of exophthalmos. Dudgeon and Urquhart[10] observed degeneration and lymphocytic infiltration in the extraocular muscles of 8 of 9 patients with hyperthyroidism and noted similar changes in cardiac muscle and in the

4. Unverricht: Experimentelle Untersuchungen über die Ursache der Exophthalmos, Klin. Wchnschr. **4**:878-879 (April 30) 1925.

5. Mutch, J. R.: Pupil After Cervico-Thoracic Sympathetic Ganglionectomy: Photographic Observations in Man, Edinburgh M. J. **43**:743-746 (Dec.) 1936.

6. Pochin, E. E.: Ocular Effects of Sympathetic Stimulation in Man, Clin. Sc. **4**:79-89 (June) 1939.

7. (*a*) Naffziger, H. C.: Progressive Exophthalmos Following Thyroidectomy: Its Pathology and Treatment, Ann. Surg. **94**:582-586 (Oct.) 1931; (*b*) Progressive Exophthalmos After Thyroidectomy, West. J. Surg. **40**:530-543 (Oct.) 1932. (*c*) Naffziger, H. C., and Jones, O. W.: The Surgical Treatment of Progressive Exophthalmos Following Thyroidectomy, J. A. M. A. **99**:638-642 (Aug. 20) 1932. (*d*) Naffziger, H. C.: Pathologic Changes in the Orbit in Progressive Exophthalmos, Arch. Ophth. **9**:1-11 (Jan.) 1933; (*e*) Progressive Exophthalmos Associated with Disorders of the Thyroid Gland, Ann. Surg. **108**:529-544 (Oct.) 1938.

8. Daniel, R.: Enophthalmos Associated with Hyperthyroidism: Suggestion Regarding Other Possible Factors in Etiology, Proc. Staff Meet., Mayo Clin. **13**:683-688 (Oct. 26) 1938.

9. Burch, G. E.: Formation of Edema in Eyelids of Man: Influence of Local Tissue Pressure, Skin Distensibility, Lymph Flow, Intraorbital Pressure Gradient and Venous Pressure, Arch. Int. Med. **65**:477-498 (March) 1940.

10. Dudgeon, L. S., and Urquhart, A. L.: Lymphorrhages in Muscles in Exophthamic Goiter, Brain **49**:182-186 (June) 1926.

deltoid, rectus femoris and biceps muscles. Von Zalka [11] found an increase in size and lymphocytic infiltration in the extraocular muscles of 16 patients who died of exophthalmic goiter. These changes, which also have been described by other observers, are similar to those noted by Naffziger and Jones [7] in patients with progressive exophthalmos, "round cell infiltration, marked edema, destruction of muscle fibers and complete loss of architecture with an increase in fibroblasts and a generalized fibrosis.[7a]" Smelser [12] has stressed edema and abnormalities of tissues other than muscle in the orbit of animals—a point not emphasized in studies reported on human beings. These mechanical changes are sufficient to account for the exophthalmos in patients with spontaneous thyrotoxicosis. The primary mechanism behind these pathologic changes in the orbit is not clear, but recent work would indicate that it is related to the function

Fig. 1.—The eyes of the patient in the upper photograph measure 15 mm. from the deepest part of the lateral wall of the orbit to the point of greatest convexity of the cornea, while those of the patient in the lower photograph measure 25 mm. (left eye) and 27 mm. (right eye).

of the anterior lobe of the pituitary and perhaps of the gonads and the adrenal cortex.

One of the reasons for confusion as to the presence or absence of exophthalmos has been the failure of many clinicians to distinguish "stare," or retraction of the upper (and perhaps the lower) lid, from protrusion of the eyeball (fig. 1). The statement one hears so fre-

11. von Zalka, E.: Ueber die Veränderungen der äusseren Augenmuskeln und ihre Bedeutung bei Morbus Basedowii, Beitr. z. path. Anat. u. z. allg. Path. **92**:239-252, 1933.

12. Smelser, G. K.: The Histology of Orbital and Other Fat Tissue Deposits in Animals with Experimentally Produced Exophthalmos, Am. J. Path. **15**:341-352 (May) 1939; The Role of the Cervical Sympathetic Ganglia and Müller's Orbital Muscle in Experimental Exophthalmos, Am. J. Ophth. **22**:1201-1209 (Nov.) 1939.

quently that "the eyes snapped back after the goiter was removed" usually means that the stare disappeared; it usually does not mean that the eyeball protruded to a lesser degree. Clinical impressions of the degree of prominence of the eyes may be misleading in enophthalmos as well as in exophthalmos. For example, it has been assumed generally that enophthalmos occurs in Horner's syndrome (paralysis of the cervical sympathetic nerves) in human beings; yet Wagener [13] and Pochin [6] showed by measurement with an exopthalmometer that enophthalmos was not present consistently. This observation is confirmed in the present report. Ptosis of the upper lid and elevation of the lower lid give an illusion of enophthalmos that is readily dispelled when the eyes are observed with the lids gently closed.

Several other clinical situations may give rise to a false impression of exophthalmos. Lid lag is not infrequently associated with unilateral ptosis of an upper eyelid. The ptosis is compensated partially by elevation of the upper eyelid and the eyebrow through contraction of the frontalis muscle. This condition, associated with overaction of the contralateral levator palpebrae superioris, caused lid lag in the opposite eye. Lid lag may be seen in normal persons or in anxious patients who show evidences of sympathetic overactivity. Realization of these factors would prevent acceptance of these false clues as evidences of hyperthyroidism.

There are a number of simple clinical correlations that aid in estimating exophthalmos. The distance from the deepest portion of the lateral wall of the orbit to the point of greatest convexity of the cornea may be determined and compared with similar observations on normal persons. In persons with exophthalmos the eyes have a staring and uncomfortably prominent appearance. Palpation with the fingers gives a sensation of increased orbital resistance. Lacrimation is excessive and may be associated with conjunctival injection and subjective discomfort. Periorbital edema is common. Patients often complain of a sense of pressure behind the eyes. Edema of the sclera, although infrequent in ordinary degrees of exophthalmos, is common in patients with severe progressive exophthalmos. Due to greater lid retraction on one side, more sclera may show in one eye than in the other, but usually measurement reveals little difference in the prominence of the two eyes, although differences of 1 to 4 mm. have been noted. Impaired convergence is nearly always present in patients with exophthalmos and may be found in the absence of exophthalmos. Diplopia is rare unless exophthalmos really exists. Lid lag may be present without exophthalmos.

13. Wagener, H. P.: Enophthalmos in Horner's Syndrome, Tr. Am. Ophth. Soc. **31**:166-175, 1933.

The foregoing discussion shows that the presence of exophthalmos can be confirmed only by careful observation and by actual measurement. The instrument used in the studies reported here was the Hertel exophthalmometer [14] (figs. 2 and 3). The instrument allows the observer to measure the distance between the deepest part of the lateral wall of the bony orbit (situated at or just below the frontozygomatic junction) and the point of greatest convexity of the cornea. The two

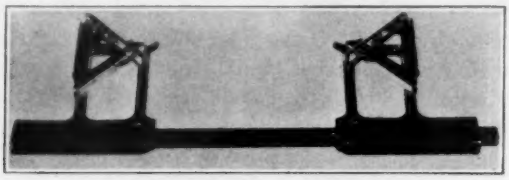

Fig. 2.—The Hertel exophthalmometer.

Fig. 3.—Manner of using the Hertel exophthalmometer. The arrow points to the reflection of the cornea.

eye pieces are so arranged that the distance between them may be varied according to the variable distances between individual pairs of eyes. Once the optimum position for placing of the eye pieces is found, the distance, which is recorded in millimeters (as "Bar at 105"), is used for all subsequent measurements on the same patient. The distance in each eye from the greatest depth of the lateral orbital wall to the anterior part of the cornea also is recorded in millimeters. The patient is seated

14. Hertel: Ein einfaches Exophthalmometer, Arch. f. Ophth. **60**:171-174, 1905.

upright with his eyes directed straight ahead while the readings are made. These measurements are made with the aid of two mirrors set at right angles (figs. 2 and 3).

The purpose of this paper is to record the measurements of the eyes of (1) 65 normal persons, (2) 106 patients with toxic diffuse goiter, (3) 52 patients with toxic nodular goiter, (4) 55 patients with nontoxic nodular goiter and (5) 2 patients before and after unilateral paralysis of the cervical sympathetic ganglions.

NORMAL PERSONS

Only a few measurements of the eyes of normal persons have been reported in the literature. The measurements on 200 normal persons published in "The American Encyclopedia and Dictionary of Ophthalmology" [15] averaged 12 to 14 mm. Ruedemann [16] obtained readings of 14 to 20 mm. on 1,000 normal persons. Wagener [18] found that in 80 per cent of 200 persons the measurements fell between 15 and 20 mm., with a range of 11 to 24 mm. Brain [17] obtained an average reading of 12.5 mm. but did not state the number of subjects examined; he later reported a maximum reading of 16 mm. (with the Hertel instrument).

My own measurements were made on 65 normal persons. The mean age was 32 years. The group consisted of 42 women (mean age 32 years) and 23 men (mean age 31.9 years). The youngest person was 19 and the oldest 51. The mean distance for each eye was 15.9 mm., and the range was 11.5 to 20 mm. (table 1).

The range of measurement in normal persons is wide. Great variations are observed in the prominence of the eyes as well as in the shape of the nose. One eye may be more prominent than the other. In addition, the inevitable error in measurement, as determined by repetition, is usually about 0.5 mm. but may be 1 mm. or more (von Birch-Hirschfeld,[18] Pochin [6]). If different observers measure the eyes of the same person, even with the same instrument, the error obviously is even

15. Wood, C. A.: The American Encyclopedia and Dictionary of Ophthalmology, Chicago, Cleveland Press, 1915, vol. 7, p. 4851.

16. Ruedemann, A. D.: The Ductless Glands as They Appertain to Eye Diseases and to Surgery, J. A. M. A. **97**:1700-1704 (Dec. 5) 1931; Exophthalmos, Cleveland Clin. Quart. **4**:66-75 (Jan.) 1937; Eye Changes Accompanying Hyperthyroidism, Ohio State M. J. **26**:318-320 (April) 1930.

17. Brain, W. R.: Exophthalmic Ophthalmoplegia, Tr. Ophth. Soc. U. Kingdom **57**:107-115, 1937. Brain, W. R., and Turnbull, H. M.: Exophthalmic Ophthalmoplegia, with Pathological Report on Ocular Muscles and Thyroid Glands, Quart. J. Med. **7**:293-323 (April) 1938.

18. von Birch-Hirschfeld: Ein neuer Exophthalmometer, Klin. Monatsbl. f. Augenh. **38**:721-726, 1900.

greater. The error is minimized by practice on the part of the operator and by careful placing of the instrument for each measurement. All the readings recorded in this study were made over a period of about five and a half years by the same observer with the same instrument.

PATIENTS WITH TOXIC DIFFUSE GOITER

This group consisted of 106 patients, all of whom had unquestioned hyperthyroidism, as determined by carefully taken histories, physical examinations and pertinent laboratory tests. All the patients whose thyroids contained nodules were eliminated from this group. The thyroids from all the patients, with the exception of those who were treated with roentgen rays, were examined pathologically.[19] The glands

TABLE 1.—*Eye Measurements* *

Spbjects	Eye †	Number of Subjects	Mean	Standard Deviation of Distribution	σMean	Range
Normal persons	OD	65	15.9	1.84	0.23	11.5-20.0
	OS	65	15.9	1.75	0.22	
Patients with nontoxic nodular goiter	OD	55	15.8	1.92	0.26	12.5-20.5
	OS	55	15.8	1.90	0.26	12.0-20.0
Patients with toxic diffuse goiter	OD	106	17.7	2.70	0.26	11.0-29.0
	OS	106	17.6	2.56	0.25	12.0-28.0
Patients with toxic nodular goiter	OD	52	16.6	2.90	0.40	11.0-22.5
	OS	52	16.5	2.74	0.38	11.0-22.5

* All measurements were made in millimeters.
† The following abbreviations have been used: OD, right eye; OS, left eye.

were cut serially, and representative sections were examined microscopically. Twenty-five of these patients were men (mean age 39.4 years), and the remainder were women (mean age 33.9 years). The mean age of the group was 35.2 years; the youngest patient was 12 years of age and the oldest 60. The mean measurement was 17.7 mm. for the right, and 17.6 mm. for the left, eye. The results of the statistical study are shown in table 1. All measurements were made before surgical or roentgen treatment had been instituted.

As in normal persons, the prominence of the eyes in patients with toxic diffuse goiter varies widely. But a sufficient number of these patients had more prominent eyes than normal persons so that the probability of the mean difference of approximately 1.8 mm. being a chance

19. A clinicopathologic study of disease of the thyroid in over 500 patients followed up for as much as six years after treatment is being carried out with Dr. Karl B. Eichorn. The patients referred to in the study reported here are included in the larger group of 500 patients.

phenomenon is less than 1 in 100,000 (table 2). In other words, these measurements confirm the presence of exophthalmos in patients with "exophthalmic" goiter. Of the group of 106 patients studied here, 71 had clinical exophthalmos. In these, the average measurement of the right eye was 18.6 mm., and that of the left, 18.5 mm. Thus, in patients with clinical exophthalmos the eyes are more prominent by measurement than in patients without clinical exophthalmos.

It is interesting to compare the results of a relatively precise method of estimating exophthalmos with clinical impressions. In this series of 106 patients 33 per cent had more prominent eyes than all but 5 per cent of the normal persons. In Cattell's series of 800 patients with exophthalmic goiter [20] 364, or 46 per cent, had exophthalmos as determined by the clinician's impression.

TABLE 2.—*Significance of Differences in Eye Measurements* of Patients with Various Types of Goiter*

Type of Goiter	Right Eye			Left Eye		
	Mean Difference	σ Difference	Critical Ratio †	Mean Difference	Difference	Critical Ratio
Nontoxic nodular and normal condition	—0.11	0.35	—0.31	—0.03	0.34	—0.09
Toxic diffuse goiter and normal condition	1.78	0.35	5.09	1.75	0.33	5.30
Toxic nodular goiter and normal condition	0.67	0.46	1.46	0.66	0.44	1.50
Toxic diffuse goiter and toxic nodular goiter	—1.11	0.48	—2.31	—1.09	0.45	—2.42

* All measurements were made in millimeters.
† A critical ratio of 5.0 means roughly that the probabilities of the difference being a chance phenomenon are about 1 in 100,000.

Seventy-eight of the 106 patients were followed up for five years or longer. Of these, 59 were treated by subtotal thyroidectomy (surgical), 16 by roentgen therapy and 3 both by surgical intervention and by roentgen therapy (of these 3, 2 had surgical treatment first and 1 had roentgen treatment first). In 38 of these 78 patients the increase in the prominence of one or both eyes was 1.5 mm. or more in an average of ten and eight-tenths months after treatment; in 19 the increase was 0.5 to 1.0 mm.; in 9 no change occurred; in 6 a decrease of 0.5 to 1.0 mm. was noted, and in 6 the decrease was 1.5 mm. or more. Of the 38 patients whose eyes became significantly more prominent, 13 had either hypothyroidism or frank myxedema. The average weight of the thyroids removed from patients whose eyes became more prominent was 2 Gm. greater than that of the glands of patients whose eyes did not become

20. Cattell, R. B.: Eye Complications in Exophthalmic Goiter: Cataracts and Exophthalmos, Ann. Surg. **100**:284-303 (Aug.) 1934.

more prominent. The changes in body weight were as follows: Those patients with a significant increase in exophthalmos gained an average of 21.5 lb. (10 Kg.); those with no change in the eyes gained an average of 18.5 lb. (8 Kg.), and those whose eyes regressed significantly gained an average of 15.6 lb. (7 Kg.). Only 3 of the 16 patients treated with roentgen rays alone had an increase of 1.5 mm. or more in one or both eyes, in contrast to 34 of 59 patients treated surgically.

The only apparent explanation for the relatively greater incidence of what may be termed mildly progressive exophthalmos in the surgically treated patients is that in general their thyroid function changes much more rapidly from a state of hyperactivity to a normal or subnormal state. On the other hand, when roentgen therapy is used, recovery is a much slower process in which even relatively rapid changes seldom are seen. Hypothyroidism did not develop in any of the patients so treated.

At the 1941 meeting of the Association of American Physicians Dr. James H. Means stated that in patients with exophthalmic goiter in whom the exophthalmos was one of the prominent symptoms the treatment should be directed toward relieving the ocular condition. He suggested that radical subtotal thyroidectomy probably should be avoided. The results reported here (presented at the 1941 meeting of the Association for the Study of Internal Secretions) bear out his contention. They certainly do not support the opinion of many surgeons that patients with severe exophthalmos should have their thyroids removed surgically rather than treated by roentgen ray "in order to prevent the progress of exophthalmos."

PATIENTS WITH TOXIC NODULAR GOITER

Since these patients fall in the group which has aroused the most discussion among physicians interested in hyperthyroidism, it is well to begin with a definition of terms. Simply stated, all 52 patients had unquestioned hyperthyroidism as well as nodular thyroids. One patient only was not operated on; she was included because all members of the Thyroid Committee at the University of California Hospital agreed on the diagnosis of toxic nodular goiter. The thyroids from all the other patients were sectioned serially; macroscopic nodules were noted, and representative sections were cut and studied microscopically. As to the definition of a nodule, it is considered to be a localized area of thyroid tissue completely surrounded by a connective tissue capsule. Most of the thyroids from these patients contained one or more nodules that were recognized grossly with ease. Most of the thyroids also showed hyperplasia within the nodules, in the rest of the gland or in both areas. One thyroid consisted of a large, hyperplastic nodule which comprised over

90 per cent of the total amount of thyroid tissue present; no signs of hyperplasia were noted in the remaining tissue.

The mean measurements of the eyes in this group were 16.6 mm. for the left eye and 16.5 mm. for the right one. Thus, the eyes of patients with toxic nodular goiter are more prominent than those of normal persons. But this difference is of only borderline significance, since it could occur by chance thirty times out of a hundred.

Twenty-seven of these patients, 25 women and 2 men, were followed up as much as fifty-four months. The mean age was 44.7 years; the 2 men were 37 and 54 years of age, respectively. Table 1 gives the statistical analysis. Eight patients' eyes became 1.5 mm. more prominent in an average of eleven and a half months after subtotal thyroidectomy; 11 patients' eyes became 0.5 to 1.0 mm. more prominent in an average of four and a half months; the eyes of 6 showed no change, and the eyes of only 2 showed a decrease of 1.5 mm. or more in an average of thirty-eight months after treatment.

On the whole, the patients in this group apparently had less exophthalmos than those with toxic diffuse goiter. Many explanations have been offered for this difference. Marine [21] expressed the opinion that the gonads must be active in order to produce experimental exophthalmos in rabbits. If gonadal activity becomes important in the human being, the older age of the patients might explain the lesser tendency to have exophthalmos. As stated, the average age of patients in this group was 44.7 years (range, 17 to 70), and, all but 2 being women, many of them were past the menopause. However, this explanation is not impressive when one sees from a review of the data that of the 8 patients (all women) whose eyes became significantly more prominent after operation, the youngest was 24 and the others were 42, 46, 49, 50, 55, 60 and 70 years of age, respectively. In general, if persons with hyperthyroidism have nodular goiter, the disease is of considerable duration and probably not severe, as evidenced by the failure of these patients to seek medical care early. The longer and milder course may allow for compensatory adjustments which prevent extensive orbital changes that might result in severe degrees of exophthalmos. It is apparent that these data permit no final answer. Indeed, one can only speculate on it on the basis of the results noted.

PATIENTS WITH NONTOXIC NODULAR GOITER

This group comprised 55 patients, all of whom had had subtotal or partial thyroidectomy and showed no signs or laboratory evidence of hyperthyroidism. The thyroids were studied pathologically as described

21. Marine, D.: Pathology and Physiology of Exophthalmos, Ann. Int. Med. **12**:443-453 (Oct.) 1938.

in the section on toxic nodular goiter, and all were found to contain encapsulated nodules by macroscopic and microscopic examination. Forty-nine of these patients were women whose average age was 42.32 years (range, 10 to 68), and 6 were men whose average age was 41.66 years (range, 26 to 64). The average age for the group was 42.25 years. Table 1 shows the number of patients, the mean measurements of the eyes, the standard deviation of this mean and the range. The conclusion was that the eyes of patients with nontoxic nodular goiter are no more prominent than those of normal persons.

Twenty-three of these patients were followed up for as long as thirty-five months after operation. In 3 the increase in the prominence of the eyes was 1.5 mm. or more in an average of nine and six-tenths months after operation (range, two and three-tenths to nineteen months); in 10 the increase was 0.5 to 1.0 mm.; in 2 no change occurred;

TABLE 3.—*Measurements of Eyes Before and After Unilateral Paralysis of the Cervical Sympathetic Ganglions*

Time	Position of Eye Pieces in Ophthalmometer	Right Eye, Mm.	Left Eye, Mm.
Before injection of right stellate ganglion.....	Bar at 107	18.5	17.0
20 minutes after.....	Bar at 107	18.5	16.5
40 minutes after.....	Bar at 107	18.0	16.5
Before injection of right stellate ganglion.....	Bar at 103	17.5	16.5
25 minutes after.....	Bar at 103	17.5	16.5

in 7 a decrease of 0.5 to 1.0 mm. was noted, and in 1 a decrease of 1.5 mm. occurred.

There is no apparent explanation for the increase in the protrusion of the eyes (significant or otherwise) in these patients. It was not due to gain in weight, for many of these patients showed no significant increase in weight. Indeed, many of them also were put on reducing diets (adequate in protein, minerals and vitamins), and lost weight as part of the general program of treatment.

PATIENTS WITH UNILATERAL PARALYSIS OF THE CERVICAL SYMPATHETIC GANGLIONS

In order to measure any possible change in the prominence of the eyes following paralysis of the cervical sympathetic ganglions measurements were made before and after unilateral injection of procaine hydrochloride into the cervical sympathetic ganglions of 2 patients; 1 was a 39 year old man with rheumatic heart disease, a nontoxic goiter and pulmonary embolism, and the other was a 56 year old woman who had hypertensive heart disease and pulmonary embolism. Table 3 gives the results of this study.

At the time when the eyes of both patients were measured after injection into the stellate ganglion, a clearcut Horner's syndrome was evidenced clinically by miosis, ptosis of the lid, conjunctival injection and increased warmth of the arm on the side of the body on which the injection was done (the right in each case). According to the unbiased opinion of 2 observers, the eye on the affected side appeared enophthalmic in each case; but this was not borne out by the measurements. I previously had measured the eyes of several patients who had Horner's syndrome from tumors that caused paralysis of the cervical sympathetic ganglions and had been struck by the fact that the enophthalmos was apparent rather than real. In these patients the eyes had not been measured before Horner's syndrome had manifested itself. The results of the measurements both before and after paralysis of the cervical sympathetic nerves agree with the data reported by Pochin [6] and Wagener.[13]

COMMENT

Stare and exophthalmos are two different manifestations that may occur as part of the syndrome associated with hyperthyroidism. The most likely cause of exophthalmos is a change and increase in the size of the extraocular muscles and the tissues of the orbit which, situated in an area enclosed on all but one side, cause proptosis of the eyeball. Progressive exophthalmos is the most extreme result of these pathologic changes which are found to some degree in the majority of patients suffering from hyperthyroidism. It would seem from these studies that in most thyrotoxic patients treatment of the hyperthyroidism itself does not cause sufficient regression of the pathologic processes in the orbital tissues to result in a regression of the exophthalmos. In fact, the majority of these patients have what might be termed a mildly progressive exophthalmos which can be determined better by actual measurement of the prominence of the eyes than by clinical observations. Nevertheless, many clinicians even without recourse to measurements have felt that the exophthalmos did not improve. In some patients the eyes may become more prominent after treatment and then regress to a certain degree. A decrease only in the measurable exophthalmos following subtotal thyroidectomy occurs in less than 10 per cent of the thyrotoxic patients. Recently Grace and Weeks [22] reported no change in exophthalmos following subtotal thyroidectomy in 80 patients with toxic goiter.

The eyes of some normal persons are as prominent as those of patients with hyperthyroidism but usually do not show abnormalities of the orbital tissues, stare or lid lag. Unlike the eyes of thyrotoxic

22. Grace, R. V., and Weeks, C.: Surgery of the Thyroid in a Large Municipal Hospital, Ann. Surg. **113**:496-507 (April) 1941.

patients with exophthalmos, which give the impression of being pushed forward, the eyes of normal persons may be described as not uncomfortably prominent. However, the borderline between normal and abnormal may be as difficult to determine by measurement as by less precise clinical observations. This is illustrated in figure 4. It is apparent that the exophthalmometer is only an aid in the study of exophthalmos. If measurements of eyes of patients with exophthalmic goiter can dispel false clinical impressions, they may pave the way to further investigative work that will allow a more satisfactory solution to this problem.

SUMMARY

No reports have appeared in the literature concerning the changes that occur in the eyes of patients with various types of thyroid disease which have been measured before and after treatment with the aid of an exophthalmometer. According to the studies reported here, the eyes

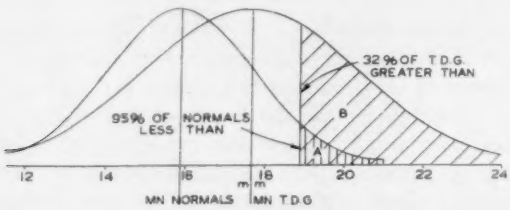

Fig. 4.—Distribution curves for eye measurements in normal persons and in patients with toxic diffuse goiter (T. D. G.). The more coarsely shaded area indicates the percentage of patients with toxic diffuse goiter whose eyes were more prominent than those of all but 5 per cent of the normal persons. The figures on the abscissa give the measurements in millimeters from the deepest point of the lateral wall of the orbit to the point of greatest convexity of the cornea.

of patients with nontoxic nodular goiter are no more prominent than those of normal persons. Patients with toxic nodular goiter tend to have more prominent eyes than normal persons but not as prominent as patients with toxic diffuse goiter. The eyes of patients with toxic diffuse goiter are significantly more prominent than those of normal persons or of patients with nontoxic nodular goiter.

The eyes of over 50 per cent of the patients with toxic diffuse goiter become measurably more prominent after subtotal thyroidectomy; they become less prominent in only a small percentage of persons. These observations are contrary to the opinion of most surgeons who have relied on clinical impressions as to the state of exophthalmos before and after treatment. It is apparent that loss of the stare associated with hyperthyroidism does not necessarily mean a decrease in exophthalmos.

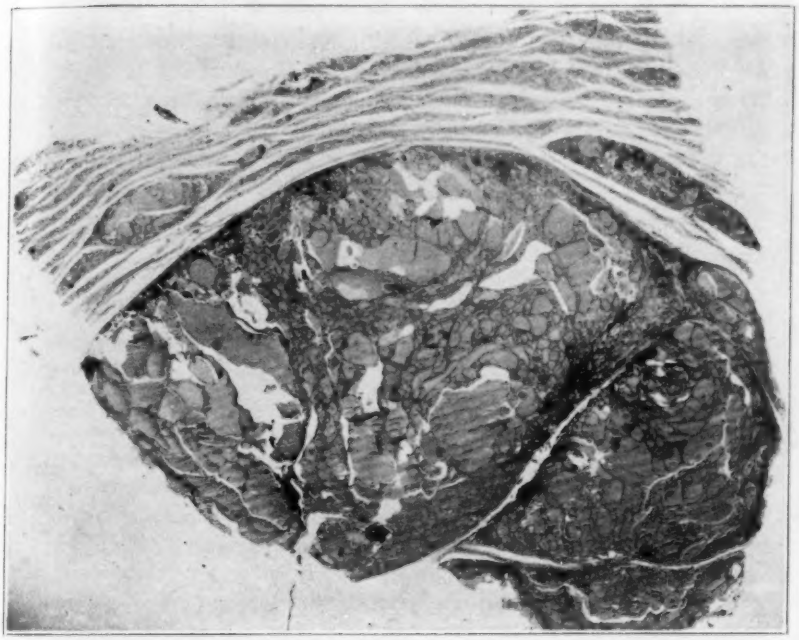

Fig. 5.—Photomicrograph of a section of thyroid from a patient with nodular goiter and hyperthyroidism of long duration.

Fig. 6.—Photomicrograph of a section of thyroid from a patient with nontoxic nodular goiter of many years' duration.

The eyes of thyrotoxic patients treated by roentgen rays show less tendency to increase in prominence. It is suggested, therefore, that for patients with hyperthyroidism in whom exophthalmos is severe, roentgen therapy is more desirable than surgical subtotal thyroidectomy. Furthermore, as also intimated by Dr. James H. Means, it is advised that the treatment in this particular group be directed toward preventing the occurrence of malignant exophthalmos.

NOTE.—Since this paper was submitted for publication Aird [23] and Hertz, Means and Williams [24] have made pertinent reports.

University of California Hospital.

23. Aird, R. B.: Experimental Exophthalmos and Associated Myopathy Induced by the Thyrotropic Hormone, Ann. Int. Med. **15**:564-581 (Sept.) 1941.

24. Hertz, S.; Means, J. H., and Williams, R. H.: Graves' Disease with Dissociation of Thyrotoxicosis and Ophthalmopathy, West. J. Surg. **49**:493-498 (Sept.) 1941.

UNUSUALLY HIGH INSULIN REQUIREMENTS IN DIABETES MELLITUS

REPORT OF A CASE

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There is no definite dextrose-insulin ratio applicable to all persons with diabetes. The amount of insulin needed to control the defective carbohydrate metabolism of any one patient must be determined empirically and may vary from time to time. Although diabetic persons with large insulin requirements are encountered infrequently, a number of cases of such requirement have been reported since the introduction of the hormone in 1922. These cases may be divided into two groups. In one the large insulin requirement is associated with some recognizable complication, such as diabetic ketosis, an infection, an endocrine disorder, hepatic disease or some other intercurrent illness. In the second there is no definite cause to account for the large amount of insulin that must be administered. This group, though small, includes some of the most extreme examples of huge insulin need.[1] Clinical and postmortem studies in such cases have revealed little to explain the pathogenesis of the insulin-resistant state. This report deals with a case of diabetes mellitus with a large insulin requirement, the cause of which could not be determined. A review of the literature revealed only 1 other case[1b] in which the maximum twenty-four hour dose (3,250 units) exceeded the greatest amount (2,795 units) administered to this patient. Of unusual interest was the complete disappearance of the excessive need for insulin six months after its sudden onset.

From the Second Medical Service and the Diabetic Clinic, Mount Sinai Hospital.

1. (*a*) Glassberg, B. Y.; Somogyi, M., and Taussig, A. E.: Diabetes Mellitus: Report of a Case Refractory to Insulin, Arch. Int. Med. **40**:676-685 (Nov.) 1927. (*b*) Wiener, H. J.: Diabetic Coma Requiring an Unprecedented Amount of Insulin, Am. J. M. Sc. **196**:211-217 (Aug.) 1938. (*c*) Glen, A., and Eaton, J. C.: Insulin Antagonism, Quart. J. Med. **7**:272-291 (April) 1938. (*d*) Marble, A.: Insulin Resistance, Arch. Int. Med. **62**:432-446 (Sept.) 1938. (*e*) Regan, J. F.; Westra, J. J., and Wilder, R. M.: Insulin Resistance: Report of a Case, New England J. Med. **223**:745-750 (Nov. 7) 1940. (*f*) Martin, W. P.; Martin, H. E.; Lyster, R. W., and Strouse, S.: Insulin Resistance: Critical Survey of the Literature with the Report of a Case, J. Clin. Endocrinol. **1**:387-397 (May) 1941.

REPORT OF CASE

A 60 year old Polish-born married Jewess was admitted to Mount Sinai Hospital on Jan. 22, 1940 for control of diabetic ketotic acidosis. She had 6 children living and well. She stated there was no family history of diabetes. Her past history was not remarkable except for an appendectomy in 1926.

In 1930, ten years before admission, glycosuria had first been discovered. Dietary restrictions alone had served to control the glycosuria for the next seven years. In 1937 she had had an attack of pneumonia, which precipitated a diabetic ketotic coma. Since that time she had required 10 units of protamine zinc insulin once daily. About one month before admission, polyuria, polydipsia and persistent glycosuria had developed. Her insulin dosage was gradually increased to 40 units daily. She lost weight and complained of headaches and generalized aches and pains. At times she seemed slightly irrational. After several days of nausea and increasing drowsiness, she presented herself for admission to the hospital.

On physical examination at the time of admission the patient was thin, flushed and drowsy. She was fully conscious, however, and responded well to questions. The tension of the eyeballs seemed normal. Ophthalmoscopic examination revealed hard white exudates typical of a diabetic retinopathy in each macular region. The heart was slightly enlarged to the left. There was a soft systolic murmur over the entire precordium, best heard over the base. The blood pressure was 200 systolic and 100 diastolic, measured in millimeters of mercury. No abnormalities of the lungs were noted. The abdomen was scaphoid, and the liver was not palpable. Both calves were tender on pressure. There were varicosities on each leg, with an area of eczema on the lateral aspect of the lower part of the left leg. There was no edema. A neurologic examination revealed depressed knee and ankle jerk reflexes in both legs and mild weakness of the extensors of the feet and the adductors of the thighs.

On admission the urine gave a positive reaction (4 plus) for reducing sugars with Benedict's reagent. The sodium nitroprusside test for acetone yielded a positive reaction (3 plus). The heat and acetic acid test for albumin gave a 3 plus reaction. Microscopic examination disclosed many clumps of white cells and occasional red cells and granular casts. The hemoglobin concentration was 75 per cent (Sahli 14.5 Gm. standard). The white cell count was 6,600 per cubic millimeter. A differential count of the stained smear showed 36 per cent polymorphonuclears, 57 per cent lymphocytes, 5 per cent monocytes and 2 per cent eosinophils. The sedimentation time for 18 mm. (Linzenmeier) was thirty minutes. The Wassermann complement fixation reaction was negative. The blood per hundred cubic centimeters contained 455 mg. of sugar, 10 mg. of urea nitrogen and 415 mg. of total cholesterol. The carbon dioxide content was 37.5 volumes per cent.

The clinical impression was moderate diabetic ketotic acidosis, diabetic retinopathy, peripheral neuropathy, essential hypertension and generalized arteriosclerosis.

Course and Treatment.—The patient was given fluids by mouth and 120 units of unmodified insulin in divided doses in twenty-four hours. At the end of this period the urine was free of sugar but still contained a trace of acetone occasionally. Although she complained of abdominal cramps and had frequent stools, her general condition was considered good. She took fluids well and was served a full diabetic diet of 150 Gm. of carbohydrate, 80 Gm. of protein and 60 Gm. of fat. During the next forty-eight hours (January 24 and 25) she had no acetonuria and slight glycosuria on 40 units of regular insulin daily.

On the fourth day of hospitalization (January 26) mild ketonuria and moderate glycosuria occurred despite 55 units of insulin. On the fifth day (January 27)

the content of sugar in blood drawn while the patient was fasting was 455 mg. per hundred cubic centimeters. She was again given 55 units of insulin, with the persistence of glycosuria (3 to 4 plus) and slight acetonuria in the late evening hours. On the sixth day (January 28) she was given 30 units of protamine zinc insulin before breakfast. Toward evening a large amount of acetone was found in the urine, and 60 additional units of regular insulin was given as well as an infusion of 1,750 cc. of 5 per cent dextrose in physiologic solution of sodium chloride.

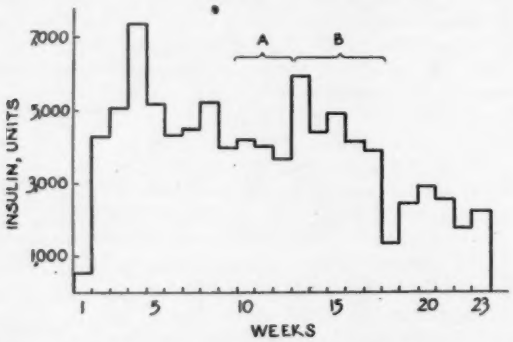
TABLE 1.—*Insulin Dosage, Fluid Balance and Degrees of Glycosuria and Acetonuria on the Ninth and Tenth Days of Hospitalization of a Diabetic Patient with a Large Insulin Requirement*

Time	Insulin Dose, Units*	Intravenous Fluid Intake, Cc.	Urine Output, Cc.	Glycosuria		Acetonuria	Comment
January 31							
6:00 a.m.	50 (protamine zinc insulin)	200	300	4+		4+	Irrational
7:00	30	300	...	4+		4+	
10:30	20	500	300	4+		4+	Incontinent of urine
2:00 p.m.	..	400	300	4+		4+	
3:00	30	...	400	4+		4+	
4:00	50	...	350	4+		4+	Infusion band torn off by patient
5:00	100	...	530	4+		4+	
				%	Gm.		
6:00	30	...	500	2.9	15	4+	Response to name
7:00	50	400	400	3.1	12	4+	Physiologic solution of sodium chloride given intravenously in place of 5% dextrose in saline solution or lactate-Ringer's solution
7:30	100						
8:00	100	250	300	3.0	9	4+	
9:00	200	275	320	3.0	9.6	4+	Patient responding better
10:30	200	275	300	3.0	9	4+	
11:30	200	...	200	2.9	6	4+	Some fluid taken by mouth
February 1							
12:30 a.m.	200	300	200	2.9	6	4+	
1:30	200 (i.v.)	300	150	2.5	3.8	4+	No change
2:30	200 (i.v.)	300	150	2.3	2.7	4+	Still confused
3:30	200	300	100	1.8	1.8	4+	
4:30	200	600	100	1:0	1.0	3+	Talk more rational
5:30	200	800	100	0.6	0.6	2+	
6:30	...	600	220	0	0	Trace	5% dextrose in physiologic solution of sodium chloride given intravenously
7:30	100 (protamine zinc insulin)	200	160	0	0	Trace	Considerable fluid taken by mouth
8:30	50	...	170	0	0	0	

* Unless otherwise specified regular insulin was administered.

On the seventh day (January 29) the ketonuria continued unabated. The patient complained of weakness and drowsiness and appeared dehydrated. She was given 30 units of protamine zinc insulin, 120 units of regular insulin and a continuous infusion of 3,950 cc. of 5 per cent dextrose in saline solution alternating with lactate-Ringer's solution, but the ketonuria did not subside. On the eighth day (January 30) the insulin was increased to 50 units of protamine zinc insulin and 180 units of regular insulin, without noticeable benefit. The intravenous fluid intake remained at 3,000 cc. During the subsequent twenty-four hours she became stuporous. Analysis of the blood on the morning of the ninth day (January 31) showed a sugar content of 300 mg. per hundred cubic centimeters and a carbon dioxide content of 27 volumes per cent. During the first twelve hours of the ninth

day she was given a total of 310 units of insulin (table 1). A total of 1,400 cc. of 5 per cent dextrose in saline solution and lactate-Ringer's solution was given intravenously. The degree of ketonuria (4 plus) was unaffected, and the patient's fluid balance remained negative. Because of the refractory ketosis insulin was increased rapidly to 200 units per hour, and 2,000 units was given in a ten hour period. Two 200 unit doses were given intravenously. At the same time the intravenous fluid was changed to physiologic solution of sodium chloride, and 4,600 cc. was given in twelve hours. Throughout the entire period the patient could be aroused, and at times she took small amounts of fruit juice by mouth. Her blood pressure varied between 128 and 160 systolic and remained at 70 diastolic, measured in millimeters of mercury. She gradually became less stuporous, and her urine showed less sugar and acetone (2 plus). Finally, sugar and acetone disappeared from the urine, and there was a striking fall in the urine output, indicating an increased ability to retain fluid. During the last twenty-four hours of this ketotic episode the patient received 2,360 units of insulin and 6,000 cc. of fluid by vein. On the eleventh day (February 2) her urine was free of sugar



The weekly total doses of insulin administered during hospitalization. *A*, the period of roentgen irradiation over the pituitary (March 26 to April 17). *B*, the period of lipocaic therapy (April 21 to May 24).

and acetone until the late afternoon after a dose of 100 units of protamine zinc insulin. With the reappearance of dextrose and a faint trace of acetone in the urine 450 units of unmodified insulin was given in divided doses until the urine cleared. On the twelfth day (February 3) the sugar content of blood drawn while the patient was fasting was 70 mg. per hundred cubic centimeters, the blood content of carbon dioxide was 47.1 volumes per cent and a single dose of 100 units of protamine zinc insulin before breakfast kept the urine free of dextrose and acetone.

The subsequent course was characterized by the continuation of the need for large doses of insulin (figure). The daily dose fluctuated, and a plateau of 1,000 units of protamine zinc insulin and regular insulin a day was reached during the fourth week of hospitalization. As much as 2,500 units of insulin during a single day (February 22) was necessary to eliminate ketonuria during the fifth week. On a number of occasions mild symptoms of hypoglycemia developed, but the patient responded promptly to oral or parenteral administration of dextrose. Two hundred units of insulin added to or subtracted from the total daily dose had

little demonstrable effect on the course of the diabetes. On one occasion a 300 unit dose of protamine zinc insulin was doubled by mistake. Despite the 600 unit initial dose, no reduction of subsequent doses of insulin was necessary.

The patient maintained an average weekly requirement of 4,200 units of insulin during the first fifteen weeks in the hospital. The average daily dose of insulin was 700 units during the first month, 593 units in the second, 615 units in the third, 446 units in the fourth and 324 units in the fifth and last month. The total amount of insulin administered was 85,680 units.

Two weeks after admission hepatomegaly was noted, and it persisted until discharge five months later. A smooth, nontender edge of the liver could be felt 2 fingerbreadths below the costal margin. The results of hepatic function tests, described in the next section of the case report, showed no deviation from normal.

On April 16, about three months after admission, the patient's temperature rose to 101 F. and watery diarrhea developed. Several other patients in the same ward were afflicted simultaneously. After repeated culture of fecal material, Bacillus dysenteriae Flexner was isolated from this patient and some of the others. Agglutination tests for typhoid, paratyphoid and dysentery organisms gave negative results. The diarrhea subsided on symptomatic therapy within five days, and cultures of feces negative for the Flexner bacillus were obtained in twenty-two days. This intercurrent infection precipitated another attack of acidosis. The carbon dioxide content of the blood fell to 23 volumes per cent, and the blood sugar rose to 355 mg. per hundred cubic centimeters. On April 20 the insulin required to control acetonuria for a twenty-four hour period reached a total of 2,795 units. With the subsidence of the ketosis, the dose was decreased to about 600 units a day. The blood sugar fell to 75 mg. per hundred cubic centimeters, and the carbon dioxide content of the blood rose to 49.2 volumes per cent.

Five and one-half months after admission the patient's daily insulin requirement was still 350 units. Because of the sudden and unpredictable fluctuations in her diabetic status, it was felt that it could not be satisfactorily controlled at home. She was transferred to the Montefiore Hospital for Chronic Diseases on July 7.

Laboratory Data.—During the five month period of observation, considerable clinical and laboratory data were obtained in an attempt to establish the cause of the excessive need for insulin. The following data are presented to illustrate the baffling nature of the problem of insulin insensitivity.

A complete blood count by the hematologist showed a hemoglobin concentration of 65 per cent, 3,900,000 red cells per cubic millimeter and 10,000 white cells per cubic millimeter, with a differential count of 63 per cent polymorphonuclears, 31 per cent lymphocytes, 4 per cent monocytes, 3 per cent eosinophils and 5 per cent reticulocytes. There were 270,000 platelets. The cell volume was 28 per cent. There was no evidence of any blood dyscrasia. Repeated blood counts revealed nothing noteworthy.

Culture of the urine on one occasion revealed Staphylococcus aureus (group B) and on another occasion Streptococcus viridans. The mild infection of the lower portion of the urinary tract was thought to have followed the numerous catheterizations during the critical period of the patient's illness. The specific gravity of the urine during a concentration test (Fishberg) rose to 1.020. A phenolsulfonphthalein test showed 35 per cent excretion of the dye within three hours. An intravenous pyelogram revealed nothing abnormal in the upper portion of the urinary tract. There was a moderate degree of hypertrophic arthritis of the lumbar portion of the spine.

Chemical analysis of the blood revealed the following contents per hundred cubic centimeters: serum chlorides from 540 to 690 mg., calcium 8.5 mg., phosphorus 2.9 mg., phosphatase 5 King-Armstrong units, total protein 5.9 Gm., albumin 3.9 Gm. and globulin 2.0 Gm. Repeated determinations did not reveal elevation of the blood urea nitrogen. The icterus index of the blood was 3; the Takata-Ara reaction was 4 plus. The blood cholesterol varied from 300 to 530 mg. per hundred cubic centimeters, with corresponding cholesterol esters between 160 to 340 mg., a normal relation. Oral dextrose tolerance tests showed high diabetic curves.

A roentgenogram of the skull showed a normal sella turcica, no evidence of increased intracranial pressure, a calcified pineal body in normal position and calcification of the parasellar groove of the right internal carotid artery without decrease in the size of the lumen of the vessel. There was no abnormality in the bones. A neurologic consultant did not find evidence of disease of the central nervous system. There was a mild peripheral neuropathy. The spinal fluid, obtained by lumbar puncture, was clear, under normal pressure and contained 4 lymphocytes per cubic millimeter. The Pandy, Wassermann and globulin tests yielded negative reactions. The colloidal gold curve was normal. The spinal fluid contained 48 mg. of protein and 68 mg. of sugar per hundred cubic centimeters. An electroencephalogram showed no abnormality.

Gastric analysis after a Rehfuss test meal showed 60 units of free acid. Examination of the stomach and duodenum after a barium sulfate meal revealed nothing abnormal. A barium sulfate enema showed nothing unusual.

Bromsulphalein tests showed no retention of the dye in the blood stream one hour after injection. The sodium benzoate test of hepatic function likewise gave a normal result. There was no bile in the urine at any time. According to the result of Ehrlich's test a trace of urobilin was present in the urine. As noted previously, the cholesterol partition was normal, and there was no evidence of bilirubinemia at any time.

Repeated roentgenograms of the chest failed to reveal any abnormality in the lungs. The electrocardiogram showed left axis deviation and a deep Q wave in lead IV; the QRS complex was slurred and of high voltage and measured twelve hundredths of a second. The T wave in lead I was diphasic. These changes were interpreted to indicate enlargement of the left ventricle and myocardial damage. Subsequent records showed no significant changes. Venous pressure was 3.5 cm. of blood with no rise on pressure in the right upper quadrant of the abdomen. The saccharin circulation time was seventeen seconds. The basal metabolic rate was + 25 per cent on one occasion, + 23 per cent after a second trial and then ± 0 per cent.

Experimental Data.—An attempt was made to determine whether there was any substance, antagonistic to insulin, in the patient's blood serum that would affect the insulin depression curves in rabbits. This was carried out by the following two methods:

1. Four and a half cubic centimeters of the patient's serum was mixed with 20 units of insulin, incubated three days at 37 C. and injected intravenously into a fasting 2 Kg. rabbit. The sugar content of the rabbit's blood was determined while the animal was fasting and one-half, one and two hours after injection. Similar parallel control determinations were made using serum from a subject without diabetes (table 2). This method was similar to the one used by Wiener.[1b]

2. Ten cubic centimeters of the patient's serum was mixed with 0.5 unit of insulin and immediately injected into a fasting 2 Kg. rabbit. The sugar content

of the rabbit's blood was determined while the animal was fasting and twenty, forty and sixty minutes after injection. Parallel control determinations were made with insulin alone, the patient's serum alone and a mixture of insulin and serum from a subject without diabetes (table 3).

In the first test the insulin depression curve was affected similarly by the patient's serum and by the control serum. In the second test both serums apparently prevented the hypoglycemia observed when insulin alone was injected.

Both these methods failed to indicate the presence of anti-insulin substances in the patient's serum that were not present in the control serum.

Passive transfer antibody tests (Prausnitz-Küstner) were performed to determine the presence or absence of transferable anti-insulin antibodies or reagins in

TABLE 2.—*Effect of an Incubated Mixture of Serum and Insulin on the Insulin Depression Curve in Rabbits*

Time Relation of Blood Sample to Injection	Blood Sugar, Mg./100 Cc.	
	4.5 Cc. of Patient's Serum Plus 20 Units of Insulin	4.5 Cc. of Serum from a Nondiabetic Subject Plus 20 Units of Insulin
Before injection, rabbit fasting	85	100
30 minutes after	75	60
60 minutes after	75	70
120 minutes after	85	85

TABLE 3.—*Effect on a Mixture (Without Incubation) of Serum and Insulin on the Insulin Depression Curve in Rabbits*

Time Relation of Blood Sample to Injection	Blood Sugar, Mg./100 Cc.			
	10 Cc. of Patient's Serum Plus 0.5 Unit of Insulin	10 Cc. of Serum from a Nondiabetic Subject Plus 0.5 Unit of Insulin	0.5 Unit of Insulin Without Serum	10 Cc. of Patient's Serum Without Insulin
Before injection, rabbit fasting	125	100	90	105
20 minutes after	95	90	65	100
40 minutes after	90	95	45	90
60 minutes after	90	100	40	90

the patient's serum. These were done by injecting the patient's serum intradermally into a normal subject and twelve hours later injecting insulin intradermally at the same site. Equivocal reactions to regular insulin (Squibb) and crystalline insulin (Stearns) were observed; preparations of protamine zinc insulin (Lilly) and unmodified insulin (Lilly) gave no reactions. Intradermal tests with these types of insulin were unrevealing. No transferable anti-insulin antibody was demonstrated. Results of precipitin tests with the patient's serum against regular insulin were negative.

Therapeutic Attempts.—After the insulin dosage had become fairly well stabilized, several attempts were made to reduce the large requirement. The usual diet contained 150 Gm. of carbohydrate, 90 Gm. of protein and 80 Gm. of fat. Trial periods both on high carbohydrate (with carbohydrates to 300 Gm.), low fat or low carbohydrate, high fat diets did not appreciably affect the insulin require-

ment. Trial periods with special beef or pork insulin were not attempted in this case. Such attempts in the case reported by Marble[1d] had no effect on the diabetes.

Because of the well known antagonism between the pancreas and the anterior lobe of the pituitary and in view of several good results of roentgen therapy reported in the literature in cases of similar disorder, it was decided to give the patient a course of such therapy over the region of the pituitary and the hypothalamus. During the third month of her stay in the hospital, the patient was given a course of roentgen therapy over the pituitary region, with a total dose of 1,900 r. This comprised nineteen daily doses of 100 r each alternately over the right and the left temporoparietal region, centering on the pituitary, through a 10 cm. by 10 cm. port. Each dose was delivered at 200 kilovolts and 20 milliamperes, with filters of 1 mm. of copper and 3 mm. of aluminum at a focal skin distance of 60 cm. The daily insulin requirement immediately before the roentgen therapy was 550 units, immediately after it 575 units, two weeks later 600 units, one month later 580 units and two months later 350 units.

During the fourth month lipocaic, a pancreatic extract, which has been claimed to diminish fatty infiltration of the liver and improve hepatic function,[2] was given in doses of 2 Gm. three times daily for thirty-four days. The average daily dose of insulin preceding the giving of lipocaic was about 550 units while after one month of treatment it had fallen to about 350 units.

Subsequent Course.—A summary of the clinical course of the patient's illness during the six months following transfer from Mount Sinai Hospital was made available by Montefiore Hospital, where she was treated for that period.

On admission to Montefiore Hospital the patient's history and the results of her physical examination were essentially as previously described. She was given 240 units of protamine zinc insulin once daily. After one week the dose was reduced to 80 units a day. Then the protamine zinc insulin was discontinued, and the patient was given unmodified insulin in doses of 40 to 50 units three times a day. At first her requirement was labile. She had frequent hypoglycemic reactions and on other occasions glycosuria (4 plus) and acetonuria (2 plus) were present. The content of blood sugar varied up to 355 mg. per hundred cubic centimeters, depending on the extent of control of the diabetes. The urine showed albumin (3 plus) and microscopic examination revealed 5 to 10 white cells, 1 to 2 red cells and many granular casts per high power field. The basal metabolic rate was + 10 per cent on two occasions. Roentgen examination of the heart showed rounding of the left ventricle and dilatation of the aorta. The lungs were clear. There was spondylitis of the lumbar portion of the spine. A series of roentgenograms of the gastrointestinal tract revealed nothing abnormal in the stomach or small intestine. Hypermotility and streaking of the transverse colon were noted.

In October 1940 the patient had an attack of jaundice associated with pains in the right upper quadrant of the abdomen, nausea and anorexia. The stools were clay colored. The icterus index at this time was 30; the van den Bergh reaction was immediately positive. The cholesterol content of the blood was 334 mg. per hundred cubic centimeters. A diagnosis of toxic hepatitis was made. This episode subsided within three weeks. A series of roentgenograms of the gallbladder made

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2. The Present Status of Lipocaic, preliminary report of the Council on Pharmacy and Chemistry, J. A. M. A. **115**:1454-1455 (Oct. 26) 1940. Dragstedt, L. R.: The Present Status of Lipocaic, ibid. **114**:29 (Jan. 6) 1940.

on November 11 was normal. In December the patient's diabetes was well controlled with only 10 units of unmodified insulin a day. The urine contained neither sugar nor acetone. On her discharge from Montefiore Hospital on Jan. 4, 1941, the diabetes was controlled by a salt-poor diet containing 130 Gm. of carbohydrate, 80 Gm. of protein and 100 Gm. of fat and a dose of 5 units of unmodified insulin once daily.

The patient returned to Mount Sinai Hospital and has been followed by one of us (H. P.) in the outpatient diabetes clinic. Her appearance was essentially unchanged, and she still complained of weakness and generalized aches and pains. Physical examination revealed nothing new. The blood pressure was 150 systolic and 90 diastolic, measured in millimeters of mercury. The urine showed a trace of albumin, occasional casts and rare red and white blood cells. The hemoglobin concentration was 90 per cent, and the white cell count, 8,400, with a normal differential count. The patient's diabetes has been satisfactorily controlled for the last six months by one daily injection of 5 units of protamine zinc insulin and a diabetic diet containing 150 Gm. of carbohydrate, 80 Gm. of protein and 100 Gm. of fat.

COMMENT

The condition of an occasional patient with diabetes mellitus refractory to specific replacement therapy with insulin is a fascinating problem. In this case, although the clinical findings furnish no satisfactory explanation for the temporary large insulin requirement, at least three mechanisms, ketotic acidosis, infection and hepatic disease, may have been of etiologic significance and will be discussed briefly. A detailed analysis of the many factors involved in the production of insulin tolerance may be found in papers by Glen and Eaton,[1e] Marble,[1d] Pollack [3] and Martin and associates [1f] and will not be repeated in this report.

During diabetic ketotic acidosis the insulin requirement is increased by some fundamental alteration in carbohydrate metabolism. Apparently a vicious cycle is set up, for as the ketotic state becomes more severe, larger amounts of insulin are needed. In this case moderate ketosis was present for at least three days prior to the onset of the insulin-resistant phase shortly after admission, on a second occasion five weeks after admission and during the episode of diarrhea two months later. With each episode of ketosis the degree of insulin tolerance increased more rapidly than did our willingness to augment the large amounts of the hormone that were being administered. Although incomplete control undoubtedly contributed to these periods of huge insulin need, acidosis cannot explain the sustained high requirement for the entire six month period. In cases of diabetes refractory to insulin reported by Wiener,[1b] Glen and Eaton [1c] and Martin and co-workers [1f] acidosis produced sharp increases in the amounts of insulin required. It is important to emphasize

3. Pollack, H.: Conditions Associated with Unusual Requirements of Insulin, Proc. Staff Meet., Mayo Clin. **8**:453-456 (July 26) 1933.

that the appearance of ketonuria in a patient with an abnormally large insulin requirement may herald a degree of insulin insensitivity that may lead to death in diabetic coma unless the ominous significance of the acidosis is realized in time.

Infection causes an increase in the severity of diabetes mellitus and is a common cause of death in patients with the disease. According to Marble,[4] the lowered carbohydrate tolerance during infections may be due to several causes: (1) the lessened production of endogenous insulin, (2) the increased production of hormonal antagonists to insulin, (3) the destruction of insulin and (4) interference with glycogen storage. Menkin [5] has advanced the hypothesis that the increase in proteolysis incident to acute inflammation is responsible for the greater severity of diabetes during infection.

The episode of bacillary dysentery demonstrates the aggravating effect of an infection on the precarious state of carbohydrate metabolism in this case. With the onset of fever and diarrhea, the patient promptly became ketotic and the insulin requirement rose from 600 to 2,795 units. Two days later, when the ketosis had been successfully combated, the daily insulin dose returned to 600 units. The change in insulin requirement was in excess of the clinical severity of the infection and indicated the unstable state of the insulin mechanism. The possibility that a subclinical bacillary dysentery was the basis for the entire period of insulin resistance cannot be denied. However, even if this were actually the case, it could only have acted as a precipitating factor to set off a basic abnormality in insulin action, since the result was so extreme.

Patients with diabetes who also have hepatic disease may require larger doses of insulin than the average person with diabetes alone. Thrombosis of the hepatic artery with infarction of the liver was the basis for insulin insensitivity in a case reported by Pollack and Long.[6] Acute hepatitis raised the daily dose of insulin from 30 to 500 units a day in a case described by Root.[7] Cirrhosis usually results in the increased severity of diabetes mellitus, although the exact opposite has been observed also. Hemochromatosis was present in 5 of 26 cases of "insulin resistance" collected by Martin and associates.[1f] In 1 case of

4. Marble, A., in Joslin, E. P.: The Treatment of Diabetes Mellitus, ed. 6, Philadelphia, Lea & Febiger, 1937, p. 407.

5. Menkin, V.: Diabetes and Inflammation, Science **93**:456-458 (May 9) 1941.

6. Pollack, H., and Long, E. R.: Thrombosis of the Hepatic Artery with Sudden Resistance to Insulin in a Diabetic Patient, Arch. Path. **13**:530-532 (March) 1932.

7. Root, H. F.: Acute Hepatitis in a Diabetic with Severe Acidosis and Suppression of Urine, New England J. Med. **212**:545-547 (March 28) 1935.

such a disorder, reported in detail by Root,[8] the patient took 1,680 units in the twenty-four hour period before death in a diabetic coma. Hepatomegaly is a common occurrence in the severe diabetes of childhood. Under such circumstances the hepatic enlargement is due to fatty infiltration. The treatment of such a condition with betaine hydrochloride,[9] pancreatic extract[10] and protamine zinc insulin[11] leads to a decrease in the size of the liver and an improvement in carbohydrate tolerance. Mirsky and his collaborators[12] have demonstrated that the susceptibility to acidosis and coma is increased by a reduction in hepatic glycogen reserves. Himsworth[13] suggested that the liver produced a ferment, insulin-kinase, necessary to activate insulin and that in patients with hepatic disease the formation of the enzyme was reduced, with a concomitant decrease in insulin sensitivity.

Several aspects of this case, particularly the hepatomegaly and the episode of jaundice, raise the question of hepatic disease as the cause of the insulin-refractory state. This factor is difficult to evaluate because in this instance one cannot distinguish between cause and effect. Jaundice occurred when the insulin requirement had almost returned to usual levels and may have been the result rather than an indication of the cause of the defective insulin activity. Hepatic function tests (bromsulphalein excretion, sodium benzoate excretion and cholesterol partition), performed when the insulin-refractory phase was at its height, did not confirm the existence of hepatic damage. The clinical improvement following a course of lipocaic,[2] which diminishes fatty infiltration in depancreatized dogs may be cited as evidence of a hepatic effect. Evaluation of possible influence of this substance, especially in this case, is extremely difficult for reasons which will be mentioned later. It is our impression that there was only slight evidence that hepatic dysfunction was a pathogenic factor in this case of insulin insensitivity,

8. Root, H. F.: Insulin Resistance and Bronze Diabetes, New England J. Med. **201**:201-206 (Aug. 1) 1929.

9. White, P.: Diabetes in Childhood, in Joslin, E. P.: Treatment of Diabetes Mellitus, ed. 6, Philadelphia, Lea & Febiger, 1937, p. 587.

10. Grayzel, H. G., and Radwin, L. S.: Hepatomegaly in Juvenile Diabetes Mellitus Treated with Pancreatic Extract, Am. J. Dis. Child. **56**:22-32 (July) 1938.

11. Hanssen, P.: Enlargement of the Liver in Diabetes Mellitus, J. A. M. A. **106**:914-916 (March 14) 1936.

12. Mirsky, I. A.; Korenberg, M.; Nelson, N., and Nelson, W. E.: The Hepatic Glycogen Reserves in Diabetes Mellitus, Endocrinology **28**:358-367 (March) 1941.

13. Himsworth, H. P.: The Activation of Insulin, Lancet **2**:935-936 (Oct. 29) 1932.

although the possibility of a partial and obscure derangement of hepatic function is difficult to exclude on the basis of the available data.

The failure to demonstrate anti-insulin activity in the serum of this patient by the methods described does not disprove the existence of this property. Only a few tests were performed, and the proper technic for the demonstration of an insulin-neutralizing substance in the serum may not have been used. However, Wiener [1b] and Martin and co-workers,[1f] using comparable methods, were also unable to detect a serum antagonist to insulin. On the other hand, Karelitz, Cohen and Leader [14] showed that normal blood and blood from a person with diabetes both inactivate insulin and that the latter did so to a greater extent. De Wesselow and Griffiths [15] obtained similar evidence in elderly persons with diabetes and suggested that the substance in the blood of these patients that affected the insulin depression of blood sugar curves in rabbits was of pituitary origin. Glen and Eaton [1e] induced an active insulin antagonism in rabbits by injections of serum from a patient with insulin insensitivity. The antagonism was more marked if the patient had been given insulin before serum was withdrawn for the test.

The management of our patient involved two distinct problems, the control of the acute alarming episodes of ketotic acidosis and the amelioration of the persistent insulin-refractory state. Each problem was of considerable interest and will be discussed separately.

The chief therapeutic agents during ketosis were insulin, physiologic solution of sodium chloride, lactate-Ringer's solution and dextrose solution. In view of the patient's age, the evidence of arteriosclerosis, the hypertension and the electrocardiographic findings, the cautious use of intravenous therapy seemed justified to prevent an overloading of the circulation. Sufficient dextrose was given to maintain glycosuria. The guide for the administration of insulin was the presence of acetone and dextrose in the hourly specimens of urine and the general condition of the patient. In the presence of persisting acetonuria, the dose of insulin was increased rapidly until an effective level was reached at 200 units per hour for ten hours. We were prepared to raise the dose to higher levels on the assumption that control would be effected eventually if enough insulin were administered. When sufficient insulin was given, the acetonuria subsided and in the presence of overdosage of insulin, hypoglycemic reactions resulted. The results were similar to those ordinarily obtained in diabetic persons except that the amounts of

14. Karelitz, S.; Cohen, P., and Leader, S. B.: Insulin Inactivation by Human Blood Cells and Plasma in Vitro, Arch. Int. Med. **45**:546-558 (April) 1930.

15. de Wesselow, O. L. V., and Griffiths, W. J.: On the Possible Role of the Anterior Pituitary in Human Diabetes, Lancet **1**:991-994 (May 2) 1936.

insulin required were enormous. Perhaps, the administration of the total amount of insulin required in a shorter time would have resulted in a more prompt response to therapy. This experience supports the concept of Taussig [16] that in cases of insulin insensitivity the law of mass action of inorganic chemistry is valid with respect to the action of insulin. As stated by Martin and associates [1f]: "There is not necessarily any upper limit to the number of units of insulin that may be given." The chief therapeutic aim is to give enough of the hormone.

The following methods have been used to reduce the insulin requirements of patients to whom it is necessary to administer excessively large amounts of the hormone: changes in diet; change in the type of insulin [1e]; intravenous administration of phosphates [1d]; therapy with various endocrine substances, particularly dihydroxyestrin (estradiol) [17]; a low potassium diet [1e]; desensitization procedures,[18] and roentgen therapy to the pituitary area.[19]

In this case a trial of roentgen therapy over the pituitary was carried out. This method of treatment has been reported to have reduced large insulin requirements in a few cases.[20] Failures of irradiation of the pituitary to influence the amount of insulin required for control of diabetes in human beings and in dogs have also been recorded.[21] Although there was no clinical evidence of disease of the pituitary in this case, it was felt that if it was possible to depress the activity of the anterior lobe, some benefit might result, since the anterior lobe of

16. Taussig, A. E.: A Case of Diabetes Mellitus Refractory to Insulin, Tr. A. Am. Physicians **42**:166-178, 1927.

17. Footnote 1 *c* and *e*.

18. Karr, W. G.; Scull, C. W., and Petty, O. H.: Insulin Resistance and Sensitivity, J. Lab. & Clin. Med. **18**:1203-1211 (Sept.) 1933.

19. (*a*) Pieri, J., and Sarradon, P.: Diabète grave insulino-résistant. Réduction notable de l'insulino-résistance par la radiothérapie hypophysaire, Bull. et mém. Soc. méd. d. hôp. de Paris **51**:1579 (Dec. 2) 1935. (*b*) Merle, E.: Diabète grave insulino-résistant. Réduction brusque et massive de l'insulino-résistance par irradiation de la région hypophysaire, ibid. **51**:35 (Jan 21) 1935. (*c*) Cannavò, L.: Insulinoresistenza e irradiationi roentgen della regione ipofiasairo, Policlinico (sez. prat.) **43**:1099 (June 15) 1936; abstracted, J. A. M. A. **107**:541 (Aug. 15) 1936. (*d*) Barnes, B. O.; Culpepper, W. L., and Hutton, J. H.: Experimental Diabetes Treated by X-Ray Applied to the Pituitary and Adrenal Regions, Am. J. Physiol. **113**:7 (Sept.) 1935. (*e*) Selle, W. A.; Westra, J. J., and Johnson, J. B.: Attempts to Reduce the Symptoms of Experimental Diabetes by Irradiation of the Hypophysis, Endocrinology **19**:97-104 (Jan.-Feb.) 1935. (*f*) Pijoan, M., and Zollinger, R.: Observations on Carbohydrate Metabolism Following Irradiation of the Pituitary Gland, ibid. **21**:357-360 (May) 1937.

20. Footnote 19 *a*, *b*, *c* and *d*.

21. Footnote 19 *e* and *f*.

the pituitary and the pancreas have been shown to be antagonists with respect to carbohydrate metabolism. There was noticeable improvement three months after the completion of this therapy. In view of the complete subsidence of the insulin-resistant state during the subsequent three months, the possibility that roentgen therapy may have been responsible for this improvement cannot be excluded. However, judgment must be reserved, since spontaneous remission has been known to occur and because lipocaic was administered for five weeks after roentgen therapy was completed.

Lipocaic, a fat-free alcohol extract of pancreas, has been reported as a specific substance which on oral administration to depancreatized dogs decreases the fat in the blood, the fatty infiltration of the liver and the insulin requirement.[2] In this case 2 Gm. of lipocaic taken daily for thirty-four days was associated with a decrease in the size of the liver and a reduction of the insulin requirement. Unfortunately, the efficacy of this therapy cannot be established with any degree of certainty in view of the previous roentgen therapy.

The complete regression of insulin resistance of the intensity and the duration observed in this case is not common. Of 26 cases collected by Martin and associates,[1f] death occurred in 12 despite therapy, as happened in the case which the authors themselves reported, making the mortality 48 per cent in this group. Subsidence of a severe insulin insensitivity was observed by Wiener,[1b] whose patient required 3,250 units of insulin in twenty-four hours while in diabetic coma and was given 142,000 units of insulin in twelve weeks. Three years later this patient was well and required only 50 units of insulin daily. No special treatment was administered to effect this change.[22] In the case reported by Glassberg, Somogyi and Taussig [1a] the patient required 26,000 units of insulin, with peaks of 1,000 and 1,100 units in twenty-four hours, during a three month period of observation. Two months later the daily insulin dose was 100 units. At the present time, fourteen years after the episode of refractoriness to insulin, this patient's diabetes is well controlled by 50 units of regular insulin taken daily in two doses.[23] Cases of this type indicate that insulin insensitivity may be temporary and that the chief indication is to furnish sufficient insulin for long enough periods to allow the refractory phase to terminate. Death in coma seems avoidable if large enough doses are given as severe emergencies arise.

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22. Dr. Herbert J. Wiener, New York, informed us of the subsequent course of his patient and permitted us to include the information in this report.

23. Dr. A. E. Taussig, St. Louis, provided the follow-up note on his case and permitted us to make the statement of the present status of his patient.

SUMMARY

A case of diabetes mellitus in which the insulin requirement was extremely high is presented. More than 85,000 units of insulin was administered in a five and one-half month period of observation. During episodes of ketotic acidosis it was necessary to give 2,360 units, 2,500 units and 2,795 units of insulin in twenty-four hours before adequate control was accomplished. No definite cause for the insulin-refractory state could be determined. Therapeutic procedures included roentgen irradiation over the pituitary and the administration of lipocaic. It was not possible to establish a definite relation between these forms of therapy and the improvement which followed their use. The excessive insulin need subsided six months after its onset, and the patient remained mildly diabetic for the subsequent six months.

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NEUROPSYCHIATRIC DISTURBANCES IN INTERNAL DISEASE*

METABOLIC FACTORS AND ELECTROENCEPHALOGRAPHIC CORRELATIONS

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Clinical manifestations of disease are in the final analysis the result of altered physiologic or biochemical relations. This is true whether one observes the direct evidence of abnormal function or the compensatory reactions invoked to counteract abnormal forces. The central nervous system is no exception to this principle. And this is no less true whether one deals with disease directly involving the central nervous system or with the effects on it of disease having its origin elsewhere. This report is concerned with secondary effects. Neuropsychiatric complications of underlying disease may vary widely from mild aberrations of normal mood and behavior to sweeping disturbances that dominate the entire clinical picture and may obscure the disease itself.

The basis for these reactions depends primarily on the fundamental nature of brain metabolism. The central nervous system has the most exacting metabolic requirements in the body. Unlike other tissues, it is primarily aerobic in its metabolism, and it is unable to establish a significant oxygen debt. Sensitivity to oxygen lack is greatest in the cerebral cortex, which suffers irreversible damage in five to eight minutes of complete oxygen deprivation, while the medulla and spinal cord fail in twenty

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* Parts of this material were presented at a meeting of the New York Neurological Society, Dec. 3, 1940 (Margolin, S. G.; Strauss, H., and Engel, G. L.: Electroencephalographic Changes Associated with Hypersensitivity of the Carotid Sinus, Arch. Neurol. & Psychiat. **45**:889 [May] 1941. Engel, G. L., and Margolin, S. G.: Clinical Correlation of the Electroencephalogram with Carbohydrate Metabolism, ibid. **45**:890 [May] 1941) and at a meeting of the New York Academy of Medicine, Section of Neurology and Psychiatry, and the New York Neurological Society, Jan. 7, 1941 (Engel, G. L., and Margolin, S. G.: Neuropsychiatric Disturbances in Addison's Disease and the Role of Impaired Carbohydrate Metabolism in Production of Abnormal Cerebral Function, ibid. **45**: 881 [May] 1941).

to thirty minutes.[1] Other tissues can survive complete oxygen lack for hours. Carbohydrate provides the major substrate capable of sustaining normal activity. Fat and protein derivatives cannot be substituted for dextrose.[2] The respiratory quotient of the mammalian brain is 1.0.[3] Storage of carbohydrate as glycogen is extremely small and does not represent a significant reserve.[5]

Closely correlated with its metabolism is the electrical activity of the brain. The electroencephalograph records brain potentials through the scalp and thereby reflects the behavior of the brain in its internal environment. Changes in metabolic factors, such as oxygen tension or availability of dextrose, are quickly reflected in the electroencephalogram.[6] Sensitivity to oxygen lack is exquisite, fourteen to fifteen seconds of complete anoxia being sufficienf to abolish completely the electrical activity of the cortex.[6b] Shifts in electrolyte balance, p_H and particularly carbon dioxide tension significantly influence the brain waves.[7] This prompt response to alterations in the internal environment of the brain provides a convenient means by which the physiologic effects of disease in remote areas may be detected and correlated with clinical observation.

In this report we are concerned chiefly with processes which interfere with proper transport and utilization of oxygen and dextrose, the two most important substances involved in cerebral metabolism. Only representative cases in each group are presented. Naturally, this covers only a small proportion of etiologic factors, but in principle a fundamental pathophysiologic basis for a more general phenomenon is provided.

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2. Corcoran, A. C., and Page, I. H.: Carbohydrate Metabolism of Brain, Enzymologia **9**:10, 1940.

3. Himwich, H. E., and Nahum, L. H.: The Respiratory Quotient of the Brain, Am. J. Physiol. **101**:446, 1932.

4. Deleted by authors.

5. Kerr, S. E., and Ghantus, M.: Carbohydrate Metabolism of Brain, J. Biol. Chem. **116**:9, 1936.

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OXYGEN LACK

Insufficient oxygenation for cerebral needs may result from cerebral anemia, in which the blood supply is diminished, and from cerebral anoxemia, in which the oxygen saturation of the blood is inadequate for cerebral needs. These two conditions cannot always be sharply divided. Both may be observed in the acute and the chronic state.

Acute Cerebral Anemia.—Acute cerebral anemia is usually due to sudden alterations in the general or the local circulation. When change is general, the manifestations are likely to be brief and to occur in the erect posture. Etiologic factors are many, but only those types which can be easily reproduced lend themselves readily to study. Hypersensitivity of the carotid sinus reflex is a convenient example which can be used in the study of a rather general phenomenon.

Thirty instances of hypersensitive carotid sinus reflex were observed. In 22 cases the patients complained of episodes of weakness, dizziness, faintness, confusion or syncope. These symptoms could be reproduced by massage or compression of the carotid sinus. Of this group, 21 cases were found to represent the cardioinhibitor (vagal) type of reflex. This reaction could be abolished by atropine. In the twenty-second case the patient had a pure depressor type, syncope following a marked fall in blood pressure, without slowing of the pulse. This could not be prevented by atropine, ephedrine, alpha-N-dimethyl-p-hydroxyphenethylamine (paredrinol), p-hydroxy-α-methylphenethylamine (paredrine), amphetamine or desoxycorticosterone acetate. Both of these types represented instances in which a sudden change in cardiovascular dynamics precipitated a critical decrease in cerebral blood flow.

Simultaneous electroencephalographic and electrocardiographic tracings were obtained in 7 cases of the vagal type, and in 1 case of the depressor type, of hypersensitive carotid sinus reflex during stimulation and before and after the administration of atropine. In the vagal group stimulation resulted in the development of an asystole of two to thirteen seconds. Onset of asystole was usually followed by hyperpnea and then by the characteristic clinical manifestations of weakness, faintness, dizziness, confusion and syncope. Simultaneously, the electroencephalogram revealed a diffuse, unlocalized burst of irregular, 3 to 6 per second waves of moderate potential, persisting for a few seconds and sometimes followed by a period of random low voltage activity. In a few cases when asystole was unusually prolonged syncope would be followed by a generalized convulsion. In such instances the electroencephalogram showed rapid high potential spikes, probably of muscle origin, superimposed on the slow waves. When the vagal cardioinhibitor reflex was blocked by atropine, no symptoms or electroencephalographic changes occurred. In the case of the depressor reflex similar electroencephalographic changes

were noted. These coincided with the development of symptoms and occurred during the rapid fall in blood pressure. Hyperpnea was again the first reaction. In all these cases the development of symptoms was more prompt and constant in the erect position.

In all the remaining 8 cases the patients exhibited symptoms that were suggestive of involvement of the central nervous system. These included focal or generalized convulsions, episodes of aphasia, motor weakness and dysesthesias. Neurologic examinations revealed nothing significant. Manual stimulation of the carotid sinus reproduced symptoms which were specific and constant in each case. In this group even when bradycardia or asystole occurred and was abolished by atropine, the characteristic neurologic reaction still took place on massage of the carotid sinus in spite of the absence of change in pulse or blood pressure. Electroencephalograms were made in 7 cases. As in the previous group, stimulation of the carotid sinus was followed by bursts of slow potentials during which the clinical manifestations characteristic for each patient occurred. No clinical manifestations became apparent unless the electroencephalographic changes occurred. The characteristic specificity of focal responses in the presence of a diffuse dysrhythmia suggested that in these cases there was an underlying focal area of diminished threshold which became clinically manifest if the reaction was not dominated by syncope or a generalized convulsion.

A hypersensitive carotid sinus reflex is generally secondary to disease directly or indirectly involving some portion of the reflex arc. Thus, it is frequently associated with generalized, cerebral and coronary arteriosclerosis and with local disease of the carotid arteries.[8] The cardioinhibitor type is sometimes associated with disease of hollow viscera, notably the gallbladder.[9] When neurologic symptoms are found to be reproducible by stimulation of the carotid sinus, other primary etiologic factors must still be considered.

Two illustrative cases are briefly presented.

Case 1.—S. S., a 46 year old man, had had a cholecystectomy performed four years before admission, because of epigastric pain, nausea, vomiting, icterus and acholic stools. At operation, the gallbladder and the cystic duct contained stones and the common duct contained chalky material. After operation the patient adhered to a low fat diet and was well for one and a half years. He then had a recurrence of attacks of epigastric pain, associated with nausea, belching and marked dizziness and faintness. There was no recurrence of icterus.

Examination on admission revealed nothing unusual. The blood pressure was 110 systolic and 70 diastolic. A well healed scar was present in the right upper

8. Ferris, E. B.; Capps, A. B., and Weiss, S.: Carotid Sinus Syncope and Its Bearing on the Mechanism of the Unconscious State and Convulsions, Medicine **14**:377, 1935.

9. Engel, G. L., and Engel, F. L.: New England J. Med., to be published.

quadrant of the abdomen. There was no abdominal tenderness or masses. The electrocardiogram was normal. Roentgen examination of the abdomen failed to yield evidence of a radiopaque biliary calculus.

Stimulation of the right carotid sinus caused an asystole of five to six seconds, hyperpnea, pallor, dizziness and faintness, followed by nausea, belching and lacrimation. These symptoms were identical with those occurring during the bouts of pain. The reaction was abolished by atropine. A duodenal tube was passed, and 20 cc. of olive oil was introduced, with a good flow of bile resulting. For two days after this it was not possible to produce any response to massage of the carotid sinus. When sensitivity had returned, the patient was given a high fat diet. This was followed by a decrease in the activity of the carotid sinus reflex and considerable relief of symptoms.

Comment: This case is representative of the first group, in which a vagal type of reflex was apparently responsible for the episodic dizziness and faintness that accompanied the attacks. In this instance the sensi-

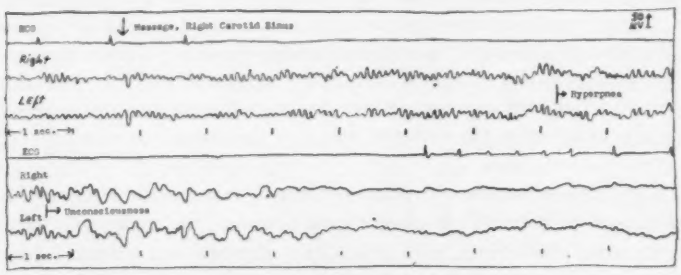

Fig. 1.—Simultaneous electroencephalogram and electrocardiogram in a case of hypersensitivity of the carotid sinus reflex of the vagal type.

tivity of the carotid sinus reflex appeared to be related to a postcholecystectomy syndrome.

Case 2.—H. Z., a 46 year old dentist, at the age of 12 had suffered an injury to the skull followed by loss of vision in the left eye. For ten years he had noted episodes of precordial pain and for two years had had fluctuating hypertension. Five months before admission he had abruptly become aware of sudden weakness occurring about ten minutes after arising in the morning. At the same time he had begun to have frequent episodes of involuntary clonic movements of the right hand and arm, which came without warning and were unrelated to any particular activity. Unassociated with this were transitory paresthesias of varying extent in the fingers of the right hand, occasionally involving the arm and the right half of the body.

On physical examination the patient appeared well developed and well nourished. The left eye showed optic atrophy, corneal scars and a left divergent strabismus. The heart and lungs were normal. The blood pressure was 140 systolic and 70 diastolic in the right arm and 105 systolic and 90 diastolic in the left arm. A systolic thrill and bruit were detectable in the left supraclavicular fossa. Numerous subcutaneous nodules, ranging from the size of a millet seed to 1 cm. in diameter,

many of which were attached to tendons, were noted. Neurologic examination revealed nothing abnormal except slight diminution of sensation for all modalities over the dorsum of the left hand.

Laboratory Data: The blood contained 500 mg. of cholesterol and 250 mg. of cholesterol ester per hundred cubic centimeters. Biopsy of a subcutaneous nodule revealed fibroxanthoma. Roentgen examination of the skull and the cervical portion of the spine showed no abnormalities. An electrocardiogram revealed normal sinus rhythm and a diphasic T wave in lead IV. Pneumoencephalography revealed moderate symmetric dilatation of the ventricular system.

Manual stimulation of the carotid sinus resulted in asystole, followed by dizziness, weakness and a focal clonic seizure involving the right upper extremity. Prolonged stimulation caused the seizure to become generalized. Atropine abolished the vagal effect, but the abnormal neurologic response and the abnormal electroencephalographic changes persisted in the absence of changes in pulse and blood pressure on massage of the carotid sinus.

Comment: This case belongs in the second group. The clinical and laboratory data justified a diagnosis of xanthomatosis. The hypersensitive carotid sinus and the focal neurologic manifestations were probably associated with the generalized vascular disease that accompanies xanthomatosis.

Acute Cerebral Anoxemia.—Acute anoxemia of sufficient extent to cause cerebral symptoms is most often a fatal complication. Instances of recurrent severe cerebral anoxemia are rare. The following case is a unique example of this condition:

Case 3.—R. I., a 15 year old girl, had a congenital cardiac lesion which had been recognized early in life. Convulsions and periods of unconsciousness had first occurred when she was a few months old. At the age of 5 years syncopal seizures had become frequent and thereafter had incapacitated her. These attacks occurred on slight exertion, on excitement and sometimes after prolonged fasting. During the attacks the patient was unconscious for one to two minutes. In the month preceding admission the patient had had at least one such spell a day.

On physical examination the patient appeared thin but well nourished. There was slight cyanosis at rest. Clubbing of the fingers and toes had occurred early. The lungs were clear. The heart was enlarged to the left and the right. The point of maximal impulse was in the sixth interspace, 11 cm. from the midline. A loud harsh murmur extended throughout systole, heard along both borders of the sternum, loudest in the third and the fourth interspace to the left. The second pulmonic sound exceeded the second aortic sound. The blood pressure was 120 systolic and 80 diastolic. Neurologic examination revealed nothing abnormal.

The report of the roentgen examination was as follows: "The heart was globular. The aorta was somewhat widened, and the pulmonary artery appeared small, suggesting the presence of pulmonary stenosis; the apex of the heart appeared unusual, being rounded and showing slight angulation, suggesting that its lower portion consisted of right ventricle."

An electrocardiogram showed regular sinus rhythm, marked right axis deviation and a QRS interval of high voltage. The carotid sinus reflex was not hypersensitive, and there was no postural hypotension.

In the ward the patient had several syncopal seizures, which were noted to occur with fear, pain, excitement and the exertion of getting out of bed. Each attack was marked by tachycardia (rate 150 to 170), which an electrocardiogram

revealed to be regular and of sinus origin. The sequence of events was, first, tachycardia, followed by increasing dyspnea and intense cyanosis and then confusion, stupor and unconsciousness. If the unconsciousness persisted for more than a minute, the patient showed clonic movements of the extremities, conjugate deviation of the eyes and rigidity. Slowing of the pulse and decrease in cyanosis always accompanied recovery. Headache and somnolence followed such attacks.

An electroencephalogram made with the patient at complete rest was entirely normal (fig. 2). After she walked 30 steps slowly, her pulse rate was 160 per minute and she was markedly cyanotic and dyspneic and somewhat dazed, torpid and confused. The electroencephalogram taken immediately showed instead of normal rhythm, slow irregular high potential delta waves (fig. 2). The record returned to normal in three and a half minutes as the patient recovered.

Comment: The clinical and roentgen findings suggested a diagnosis of tetralogy of Fallot. The mechanism of the seizures was thought to be as follows: At complete rest the heart was just capable of meeting tissue oxygen requirements, as indicated by the slight degree of cyanosis

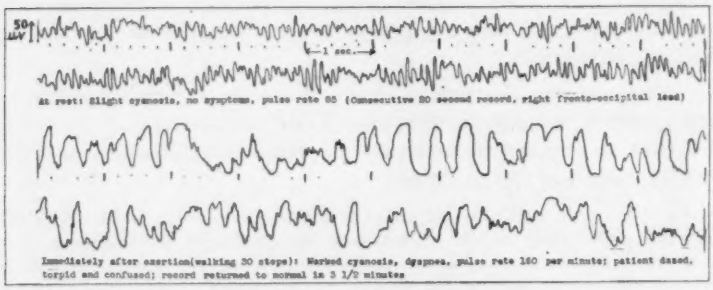
50
1 sec.
At rest: Slight cyanosis, no symptoms, pulse rate 85 (Consecutive 20 second record, right fronto-occipital lead)
Immediately after exertion(walking 30 steps): Marked cyanosis, dyspnea, pulse rate 160 per minute; patient dazed, torpid and confused; record returned to normal in 3 1/2 minutes

Fig. 2.—Electroencephalogram in a case of acute cerebral anoxemia.

and the normal electroencephalogram. During tachycardia, produced by any cardioaccelerator stimulus, such as exertion, fear or pain, the nature of the congenital defect prevented adequate quantities of fully oxygenated blood from reaching the tissues. The resultant anoxia in itself tended to increase the tachycardia. The ensuing picture was the direct result of acute cerebral anoxemia. Compensation was restored only when the cardiac rate was again slowed.[9a]

9a. Recently there has come to our attention a case of an almost identical condition reported by Hunter, in 1783 (M. Obs. Soc. Physicians London, **6**:299, 1784). The patient in this case was an 8 year old boy, whom Hunter observed until his death at the age of 13. To quote directly from the author's report: "His [the boy's] complexion had never been fresh, but always dark, or tending to black. . . . The most distressing symptoms were fits, which were always alarming, sometimes more violent and more frequent than at other times, and in general worse when he was in town than in the country; for which reason he was kept for some years almost constantly at his father's country seat. When the fit was coming upon him, he was

(Footnote continued on next page)

Chronic Cerebral Anoxemia.—The typical syndrome of chronic cerebral anoxemia is most commonly found in the end stages of chronic asthma and bronchitis, when the compensatory devices have reached their limit. Four cases in this category were observed. The ages of the patients ranged from 52 to 69 years. All gave a history of bronchitis and asthma of many years' duration and of increasing dyspnea and cyanosis preceding admission. All showed marked emphysema and diminished vital capacities, ranging from 800 to 1,300 cc. Marked secondary polycythemia was present, the red cell count ranging from 6,640,000 to 7,480,000 per cubic millimeter. The blood volumes of 2 of these patients were 159 and 167 cc. per kilogram, respectively, almost double normal. In 1 patient the arterial oxygen saturation was only 85.9 per cent three weeks before decompensation had begun.

In only 1 of these 4 cases did the patient survive. In all cases the patients had pulmonary decompensation precipitated by an acute infection of the respiratory tract. All patients entered the hospital with acute right-sided heart failure and with intense respiratory distress. The heart failure and the infection responded to specific therapy, but a predominantly cerebral syndrome persisted. Two of the patients had collapsed just prior to entry. At first the patients showed somnolence, torpor and confusion. They could be aroused, answer simple questions and obey simple commands. The 1 surviving patient overcame her pulmonary infection at this stage and thereafter recovered. In the others stupor gradually deepened, accompanied by a marked slowing of all activities and then by rigidity, hyperreflexia and occasional clonic twitches. This passed rapidly to a stage of diminishing to absent deep reflexes; loss of respiratory, cough and gag reflexes, and finally incontinence of urine and

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commonly sensible of it: he grew oppressed at his heart, became weak or faint, grew dark in his colour, and at last almost black, fell down, and seemed insensible. He commonly soon came out of the fit, with sobbing and yawning, and a sense of fatigue. Any hurry upon his spirits, or brisk motion of his body, would generally occasion a fit. And for some of the last years of his life, he had found out, by his own observation, that when the fit was coming upon him, he could escape it altogether, or at least take considerably from its violence or duration, by instantly lying down upon the carpet, on his left side, and remaining immovable in that position for about ten minutes." Hunter was fortunate in obtaining an autopsy. ". . . The cause of his complaint was then very apparent. There was a singular conformation of the heart, which allowed only a very small portion of the blood to pass through the lungs. That peculiarity was partly in the pulmonary artery, which was so small at its beginning from the right ventricle, that it would barely give passage to a small probe. But there was another peculiarity . . ., viz. the septum cordis was deficient, or perforated at the basis of the heart; so as, in the dead body, to allow my thumb (a small one) to pass across, from either ventricle to the other, the orifice of the aorta being situated so close to this perforation, as, in the action of the heart, to receive the blood from the right ventricle as well as from the left." This, of course, is a description of the combination of congenital defects now known as the tetralogy of Fallot.

feces. The suppression of the cough and the respiratory reflex established a vicious cycle that terminated in death one to two weeks from the time of entry.

In the case with recovery the electroencephalogram showed a regular rhythm, with a frequency of 7.5 to 8.0 per second, which is at the lower range of normal. In the remaining cases the electroencephalogram showed diffuse, slow, high potential waves, which were uninfluenced by opening the eyes, and a complete absence of normal alpha waves. In the earlier stages of anoxemia the waves were 5 to 6 per second in frequency and were fairly regular. With progression of the anoxemic process the record became increasingly disorganized (fig. 3, compare the record in case 4 to that in case 29). It was not possible to change the electroencephalogram or improve the patient's condition by the inhalation of 100 per cent oxygen.[9b]

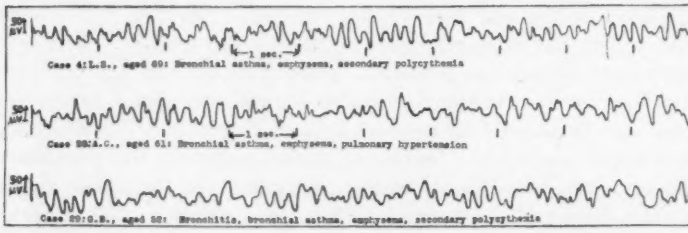
1 sec.
Case 4: L.S., aged 69: Bronchial asthma, emphysema, secondary polycythemia
1 sec.
Case 29: A.C., aged 61: Bronchial asthma, emphysema, pulmonary hypertension
Case 29: G.B., aged 62: Bronchitis, bronchial asthma, emphysema, secondary polycythemia

Fig. 3.—Electroencephalograms in cases of chronic cerebral anoxemia.

The following was typical of the group:

CASE 4.—L. S., a 69 year old man, had had severe asthma for many years. For several weeks he had noted increasing dyspnea and frequent asthmatic attacks. Two days before admission he had become much more dyspneic, and the next day edema of the legs and abdomen had appeared. Sudden collapse led to his admission to the hospital.

On physical examination the patient was acutely ill, with intense, black cyanosis and marked dyspnea. The mucous membranes were congested and cyanotic. The pharynx was injected, and there was a postnasal drip of thick, purulent material. The veins of the neck were distended, and there was a hepatojugular reflux. The chest was markedly emphysematous. The breath sounds were distant and accompanied by many sibilant and sonorous rales throughout the sticky moist rales at the bases of both lungs. There was dulness at the base of the left lung. The heart was enlarged to the left and the right. The second pulmonic sound was accentuated. The blood pressure was 170 systolic and 110 diastolic. The liver

9b. Recent studies by one of us (G. E.), making use of a more quantitative method of analysis of the electroencephalogram, have revealed that a significant degree of improvement in the electroencephalogram occurs on inhalation of 100 per cent oxygen in chronic anoxemia of pulmonary origin if the arterial oxygen saturation can be significantly raised.

was enlarged, and there was pitting edema of the legs to a point above the knees. The deep reflexes were hyperactive. The patient was torpid and responded slowly.

Laboratory examination of the blood revealed the hemoglobin concentration to be 126 per cent; the red cell count, 7,480,000 per cubic millimeter; the white cell count, 8,000, with a shift to the left; the urea nitrogen, 15 mg. per hundred cubic centimeters, and the carbon dioxide combining power, 91.5 volumes per cent. The venous pressure was 10.5 cm. of water, with a rise to 16 cm. on compression of the right upper quadrant of the abdomen. The saccharine circulation time was eighteen seconds, and the ether circulation time, eleven seconds. The vital capacity was 1,000 cc. The electrocardiogram showed left axis deviation, prominent P waves and slurring of the QRS interval in lead I.

Heart failure quickly subsided with the use of mercupurin and the limitation of fluids. However, the patient remained intensely cyanotic even with 100 per cent oxygen given by the Boothby-Lovelace-Bubulian mask. Torpor increased, but the patient could be aroused. All movements and reactions to stimuli became markedly slowed. The deep reflexes became depressed and then extinguished. There was marked muscle weakness. Respirations became more shallow; the cough reflex diminished, and he was unable to bring up the thick bronchial secretions. Multiple areas of atelectasis developed. Administration of coramine (a 25 per cent solution of pyridine betacarboxylic acid diethylamide) and bronchoscopy were ineffective, and after eleven days the patient became comatose and incontinent; he died on the thirteenth day of hospitalization.

An electroencephalogram was taken on the sixth day of his stay in the hospital, when he still could be easily aroused but showed marked retardation. It revealed fairly regular 5 to 6 per second waves of moderately high potential, which were uninfluenced by opening or closing the eyes (fig. 3, case 4).

ABNORMAL CARBOHYDRATE METABOLISM

Abnormal carbohydrate metabolism provides the basis for neuropsychiatric disturbances in another group of cases. Two types of disorder are considered. The first, Addison's disease, is an endogenous deficiency state with a well defined disturbance in carbohydrate metabolism and is represented by 8 cases. The second group of 5 cases includes a variety of toxic and deficiency states in which the chief evidence for disordered carbohydrate metabolism is a flat sugar tolerance curve with hypoglycemia but in which the nature of this disturbance is not always clear.

Addison's Disease.—The presence of a definite defect in carbohydrate metabolism which can be ameliorated by adequate replacement therapy makes Addison's disease an ideal condition for the study of cerebral response to faulty carbohydrate usage. The main features concerning carbohydrate metabolism in Addison's disease may be summarized as follows:[10] (*a*) slightly impaired absorption of dextrose from the gastrointestinal tract; (*b*) decreased ability to form new dextrose from the

10. (*a*) Long, C. N. H.; Katzen, B., and Fry, E.: The Adrenal Cortex and Carbohydrate Metabolism, Endocrinology **26**:309, 1940. (*b*) Thorn, G. W.; Koepf, G. F.; Lewis, R. A., and Olsen, E. F.: Carbohydrate Metabolism in Addison's Disease, J. Clin. Investigation **19**:813, 1940.

intermediary products of carbohydrate and of protein metabolism; (*c*) a corresponding increase in the utilization of exogenous carbohydrate at the expense of fat and protein, indicated by an elevated respiratory quotient and an increased carbohydrate appetite; (*d*) rapid exhaustion of available carbohydrate stores, including liver glycogen, particularly under fasting conditions; (*e*) markedly increased sensitivity to factors which normally lower the level of blood sugar, such as insulin or fasting, with failure of normal homeostatic mechanism to counteract the resultant hypoglycemia, and (*f*) a tendency to a low value for blood sugar during fasting and a flat sugar tolerance curve with terminal hypoglycemia.

This type of metabolic disturbance, involving both inadequate supply and inefficient utilization of dextrose, clearly represents more than simple hypoglycemia. In patients with Addison's disease symptoms of hypoglycemia may develop at much higher levels of blood sugar than in normal persons,[10b] suggesting that the threshold of cerebral reaction has been lowered. Under such circumstances it is not unexpected that neuropsychiatric disturbances are encountered commonly in persons with this disease. This was first pointed out in the original description by Addison, in 1855,[11] who thought these manifestations resulted from disturbed cerebral circulation. Some of the earlier observers were so impressed with this aspect of the disease that they considered the illness primarily one of the nervous system.[12] Klippel discussed the *encéphalopathie addisonienne*.[13] Hartman [14] repeatedly called attention to the nervous manifestations of the disease and was certain that the vital hormone affected the nervous system directly.

The incidence of neuropsychiatric disturbances in patients with Addison's disease is higher than is ordinarily realized. Of the 25 cases of this condition on record at Mount Sinai Hospital during the past ten years, signs and symptoms in 16 were striking enough to deserve comment (table 1). Review of the literature confirmed this impression. Most commonly these manifestations occur preceding or during crises and may include the widest range of abnormalities. Changes in mood or behavior not infrequently constitute the earliest clinical evidence of impending collapse. In other cases recurrent spells of bizarre behavior or episodic neurologic disturbances occur, with relatively free intervals between.[13] And there are a group of cases on record with sweeping disturbances of long standing, which show marked fluctuations from

11. Addison, T.: On the Constitutional and Local Effects of Disease of the Supra-Renal Capsules, London, S. Highley, 1855.

12. Greenhow, E. H.: On Addison's Disease, London, Longmans [and others], 1875.

13. Klippel, M.: Encéphalopathie addisonienne, Rev. neurol. **7**:898, 1899. Lebrun, R.: Contribution à l'étude de l'encéphalopathie addisonienne, Thesis, Paris, 1937.

14. Hartman, F.: The Adrenal Problem, Endocrinology **19**:633, 1935.

time to time.[15] The most characteristic feature of these disturbances is their fluctuating and episodic nature and the fact that they may include a wide variety of neurologic and psychiatric disorders. This is well illustrated in the following case:

CASE 5 (this case will be reported in detail elsewhere[16]).—The patient was a 27 year old man with known Addison's disease of seven years' duration. Crisis first appeared during the development of thromboangiitis obliterans which involved both legs. Clinical and laboratory findings at that time were typical of Addison's disease. After this he was maintained in relatively good health, except during intercurrent infections, with an aqueous adrenal cortical extract, supplied by Drs. W. W. Swingle and L. G. Rowntree, and sodium chloride. One year before

TABLE 1.—*Neuropsychiatric Disturbances in Cases of Addison's Disease Recorded at the Mount Sinai Hospital, 1930-1940*

Case No.	Age, Yr.	Clinical Manifestations
18	35	Paresthesias of fingers and toes
19	50	Irregular pupils; diminished deep reflexes; diminished vibratory sense
20	50	Nervous; irritable; markedly uncooperative; depressed
21	57	Acute paranoid psychosis; noisy; difficult nursing problem; committed suicide after discharge
22	74	Confused; depressed; negativistic
23	53	Horner's syndrome; right abdominal reflexes depressed; bilateral suprapatellar and ankle clonus; hyperreflexia
24	38	Transient paresthesias of hands and feet; hyperactive deep reflexes; uncooperative patient
25	40	Transient amblyopia
26	42	Irregular pupils, reacting sluggishly; bilateral ptosis
27	28	Acute psychosis with delirium, disorientation, delusions, hallucinations and irrational, erotic behavior
11	23	Marked depression, with suicide attempt; uncooperative; childish
12	46	Personality change, with irritability, restlessness, depression and loss of interest; patient uncooperative, surly and complaining
13	22	Collapse, followed by appearance of spastic paraplegia, with hyperactive reflexes, clonus and spastic gait
14	47	Marked depression and agitation during impending crisis
5	27	Dyskinetic syndrome; convulsions; paresthesias; scotomas; marked personality change (see text)
16	54	Tearful, rambling, agitated, depressed, uncooperative; sensation of tightness and pulling in the hands; deep reflexes markedly depressed

admission the patient began to take the extract irregularly and finally discontinued it altogether. Within a few months he began to show a decided change in personality, with irritability, unmannerliness, deterioration of habits, unexplained bursts of anger and periods of amnesia and unreality. A dyskinetic syndrome, occasionally hemiballistic and occasionally choreoathetoid; trismic speech; ataxia;

15. Porter-Philips, J. G.: Nervous and Mental Symptoms in a Case of Addison's Disease, Brit. M. J. **2**:1705, 1912. Rushton, J. G.; Cragg, R. W., and Stalker, L. K.: Spontaneous Hypoglycemia Due to Atrophy of the Adrenal Glands, Arch. Int. Med. **66**:531 (Sept.) 1940. Porot, M. A.: Psychose addisonienne; Essai de traitement chloruré, Ann. méd. psychol. **2**:665, 1937.

16. Engel, G. L., and Margolin, S.: Chronic Hypoglycemia in a Case of Addison's Disease, to be published. The patient in this case has already been the subject of two previous reports (Silbert, S.: Thromboangiitis Obliterans and Addison's Disease in the Same Patient, J. A. M. A. **108**:551 [Feb. 13] 1937. Rowntree, L. G.: Increasing Survival Time in Addison's Disease, ibid. **114**:2526 [June 29] 1940).

transient scotomas; patchy dysesthesias, and finally, convulsions made their appearance. All these manifestations showed striking fluctuation from time to time. The patient evinced a growing carbohydrate appetite, and his symptoms showed considerable variation with food habits, becoming worse after fasts. He was completely incapacitated by these symptoms and was admitted to the hospital May 3, 1940.

On physical examination the patient was well developed and well nourished, with striking pigmentation of the skin and mucous membranes. He moved about constantly in bed, showing jerky, involuntary movements of all his extremities. There were frequent twisting and arching movements of the trunk and grimaces of the face. Speech was markedly trismic; the gait, broad based and ataxic. Marked finger to nose ataxia was present. The blood pressure was 135 systolic and 85 diastolic. The heart and lungs were normal. The left great toe had been amputated. Pulsations were absent in the left leg.

Examination of the blood revealed the hemoglobin content to be 17.5 Gm. per hundred cubic centimeters; the hematocrit reading, 48.5 per cent; the urea nitrogen, 21 mg. per hundred cubic centimeters; the sugar, 75 mg. per hundred cubic

TABLE 2.—*Dextrose Tolerance Tests, Case 5*

Date	Therapy	Blood Sugar, Mg./100 Cc.							
		Fasting	½ Hr.	1 Hr.	2 Hr.	3 Hr.	4 Hr.	4½ Hr.	Comment
5/ 8	None	75	110	105	100	90	..	..	.....
5/22	Desoxycorticosterone acetate	85	125	100	85	105	..	..	.....
6/ 1	Aqueous adrenal cortical extract (Upjohn)	85	135	130	120	110	65	..	Reaction
7/19	Vitamin B complex	85	165	165	150	130	55	..	Reaction
7/26	Vitamin B complex and aqueous adrenal cortical extract (Upjohn)	85	135	140	110	100	70	..	Reaction
3/ 5	Vitamin B complex and aqueous adrenal cortical extract (Upjohn)	65	165	180	110	80	..	75	No reaction

centimeters; the chlorides, 95.6 milliequivalents per liter, and the sodium, 135.3 milliequivalents per liter.

Course: The patient was observed for a total of fourteen months. On admission it was found that he had a huge carbohydrate appetite, consuming an average of 800 Gm. of carbohydrate daily. Blood sugar values during the day ranged between 65 to 95 mg. per hundred cubic centimeters in spite of frequent feedings. Typical hypoglycemic reactions, characterized by profuse sweating, tachycardia, weakness and sudden personality change, were frequent and were associated with blood sugar levels of 45 to 75 mg. per hundred cubic centimeters. The dextrose tolerance curve on admission was flat (table 2). The patient's neuropsychiatric symptoms were transiently, but only partially, relieved by the frequent high carbohydrate feedings. Desoxycorticosterone acetate, which has little effect on carbohydrate metabolism in persons with Addison's disease,[10b] was ineffective. Definite and sustained improvement followed the use of an aqueous adrenal cortical extract (Upjohn) in a dose of 5 cc. daily. When, in addition to this, massive doses of thiamine hydrochloride (60 mg.), riboflavin (30 mg.) and nicotinamide (300 mg.) were used, an almost complete remission of the patient's presenting symptoms took place. He was able to return to normal activity and thereafter remained asymptomatic except during lapses in therapy and intercurrent infections. Associated with this clinical improvement were a decrease in daily carbohydrate intake to an average of 450 Gm. four times daily, a gain of 30 pounds (14 Kg.) in weight,

an increase in the height of the dextrose tolerance curve (table 2) and higher random levels of blood sugar (75 to 130 mg. per hundred cubic centimeters).

Electroencephalograms were taken at frequent intervals. The initial record (fig. 4) showed marked disorganization of the normal pattern, with much slow, irregular, high potential 2 to 6 per second activity. At this time it was not possible to influence this pattern more than slightly by large quantities of dextrose. As the patient's symptoms were brought under control and the carbohydrate utilization improved, the electroencephalogram showed progressive improvement. When the patient was asymptomatic, the record became normal, although the level of blood sugar at the time the record was taken was not significantly higher. Precipitation of a hypoglycemic reaction, with a fall of blood sugar to 70 mg. per hundred cubic centimeters, reproduced a record similar to the original one, but this record could now be restored to normal by the administration of dextrose.

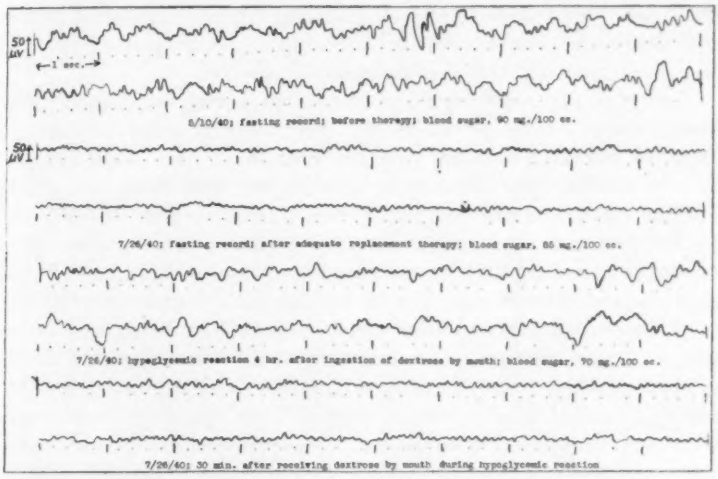
50 μv
1 sec.
5/10/40: fasting record: before therapy: blood sugar, 90 mg./100 cc.
50 μv
7/26/40: fasting record: after adequate replacement therapy: blood sugar, 85 mg./100 cc.
7/26/40: hypoglycemic reaction 4 hr. after ingestion of dextrose by mouth: blood sugar, 70 mg./100 cc.
7/26/40: 30 min. after receiving dextrose by mouth during hypoglycemic reaction

Fig. 4 (case 5).—Electroencephalograms made during the course of therapy of Addison's disease.

Comment: In this case striking neuropsychiatric symptoms were associated with a marked disturbance in carbohydrate metabolism and a diffuse abnormality in the electrical activity of the brain. The close parallel between the improvement in the clinical manifestations, the carbohydrate metabolism and the electroencephalographic activity on specific replacement therapy warrants the conclusion that they were intimately related. The electroencephalogram strongly resembles that reported for insulin hypoglycemia,[6c] but it is significant that in cases of induced hypoglycemia such records were obtained only with levels of blood sugar well under 50 mg. per hundred cubic centimeters and the records were promptly restored to normal by the administration of dextrose. The much higher levels of blood sugar in this case suggest

that the ability of the central nervous system to utilize the available sugar was also impaired. Even when the electroencephalogram had been restored to normal, a typical hypoglycemic record could be produced at a level of blood sugar of 70 mg. per hundred cubic centimeters, suggesting a lower threshold of cerebral reaction. A fuller discussion of the possible modes of action of the various therapeutic agents used in this case cannot be taken up here but will be the subject of another report.[16a]

In all cases of Addison's disease some degree of impairment of carbohydrate metabolism may be demonstrated. Cases in which it dominates the disease, however, are less commonly encountered, and the case just presented represents an unusually severe instance. Seven other cases of typical Addison's disease were studied. Four of these cases have been reported.[17] In all cases the patients were being treated with desoxycorticosterone acetate. Histories of 5 of the patients revealed significant neuropsychiatric disturbances (table 1).

Levels of sugar determined in blood drawn while the patients were fasting ranged from 50 to 95 mg. per hundred cubic centimeters. Dextrose tolerance tests are recorded in table 3. In 4 cases (15, 12, 13 and 17) the sugar tolerance curves were flat. In 3 cases (15, 14 and 12) the patients experienced hypoglycemic reactions four to five hours after receiving dextrose, sugar values at that time ranging from 55 to 65 mg. per hundred cubic centimeters. In 3 cases (11, 12 and 15) the patients gave histories suggestive of spontaneous hypoglycemic reactions.

Electroencephalograms taken under fasting conditions showed abnormalities in the spontaneous records in 5 cases. These consisted chiefly of bursts of 3 to 6 per second potentials, usually of higher voltage than the alpha waves and with no definite cortical focus (fig. 5). These waves could not immediately be influenced by dextrose but did show variation with the general condition of the patient. For example, the abnormalities in the record in case 11 (fig. 5) taken when the patient was exhibiting

16a. Since this report was submitted for publication, it has been established that this patient is also suffering from a diffuse vascular disease. This has manifested itself by albuminuria, closure of retinal vessels, preretinal hemorrhages, mild hypertension (150 systolic and 100 diastolic) and recurrent indolent ulcers, biopsy of one of which revealed the vascular lesions. The relation between this condition and the Addisonian syndrome is entirely unclear at the present time. Therapy with adrenal cortical extract (Upjohn) was discontinued in October 1941, and again the patient appeared to be unaffected thereby for several months. However, he was readmitted to the hospital in June 1942, with recurrence of convulsions, loss of 10 pounds (5 Kg.) in weight and hypoglycemia. A dextrose tolerance curve on this admission was as follows: fasting, 70 mg. per hundred cubic centimeters; one hour, 80 mg.; two hours, 70 mg.; three hours, 50 mg., and four hours, 25 mg., with a marked reaction.

17. Soffer, L. J.; Engel, F. L., and Oppenheimer, B. S.: Treatment of Addison's Disease with Desoxycorticosterone Acetate, J. A. M. A. **115**:1860 (Nov. 30) 1940.

TABLE 3.—*Dextrose Tolerance Curves and Electroencephalographic Abnormalities During Hyperventilation*

Case No.	Date	Diagnosis		Time After Dextrose Ingestion							
				Fasting	½ Hr.	1 Hr.	2 Hr.	3 Hr.	4 Hr.	5 Hr.	6 Hr.
11	7/ 9	Addison's disease....	Blood sugar, mg./100 cc.	95	150	165	135	150	115	90	85
			Percentage of 2-5 per second waves, EEG*	46	0	0	0	0	8	28	28
			Percentage of induction time†	32	100	100	100	100	80	70	80
13	7/ 9	Addison's disease....	Blood sugar, mg./100 cc.	90	105	105	70	85	95	90	90
			Percentage of 2-5 per second waves, EEG.	58	1	23	60	53	53	63	43
			Percentage of induction time.	30	99	70	26	25	26	30	25
15	8/23	Addison's disease....	Blood sugar, mg./100 cc.	80	100	100	120	95	95	65	75
			Percentage of 2-5 per second waves, EEG.	26	2	0	0	2	0	65	16
			Percentage of induction time.	68	90	100	100	86	100	40	58
14	10/10	Addison's disease....	Blood sugar, mg./100 cc.	85	135	145	130	90	55	80	75
			Percentage of 2-5 per second waves, EEG.	7	0	0	0	0	10	0	0
			Percentage of induction time.	58	100	100	100	100	45	100	100
16	3/12	Addison's disease....	Blood sugar, mg./100 cc.	90	160	180	95	100			
12	10/25	Addison's disease....	Blood sugar, mg./100 cc.	75	105	105	100	95	75	65	85
17	12/19	Addison's disease....	Blood sugar, mg./100 cc.	90	105	100	85	80			
6	11/ 1	Ulcerative colitis.....	Blood sugar, mg./100 cc.	85	100	105	95	75	65	75	
			Percentage of 2-5 per second waves, EEG.	40	0	0	0	4	10	2	
			Percentage of induction time.	43	100	100	100	72	66	90	
7	11/ 1	Anorexia nervosa....	Blood sugar, mg./100 cc.	85	110	110	100	80	65	70	70
			Percentage of 2-5 per second waves, EEG.	26	0	0	3	25	52	37	25
			Percentage of induction time.	68	100	100	86	90	52	74	88
8	9/ 5	Anorexia nervosa....	Blood sugar, mg./100 cc.	80	105	105	90	65	80		
	10/ 9	Anorexia nervosa....	Blood sugar, mg./100 cc.	85	115	135	100	100	70	80	
9	11/25	Periarteritis nodosa	Blood sugar, mg./100 cc.	90	105	120	95	65	70	80	
10	2/18	Anxiety state.....	Blood sugar, mg./100 cc.	70	105	110	100	40	60	70	

* The amount of the hyperventilation record made up of 2-5 per second waves, expressed as a percentage of the whole hyperventilation period.

† The length of time of hyperventilation before 2-5 per second waves appeared, expressed as a percentage of the whole time of hyperventilation. A value of 100 per cent means no 2-5 per second waves appeared by the end of the hyperventilation period.

early evidences of insufficiency, including hypoglycemic episodes, disappeared completely several months later when her general condition and appetite were excellent.

The effects of hyperventilation on the electroencephalogram were studied in 6 cases (a preliminary report of this study has already been made [18]). In 5 of these the patients when fasting showed an abrupt appearance of long bursts of high potential (75 to 175 microvolts) waves, of a frequency of 2 to 5 per second, most often 2 to 3 per second. In some instances these bursts bore some resemblance to the wave and spike pattern of petit mal. The types of waves are illustrated in figure 6. The length of time of hyperventilation necessary to bring out these potentials was short, nineteen to fifty-eight seconds. This interval

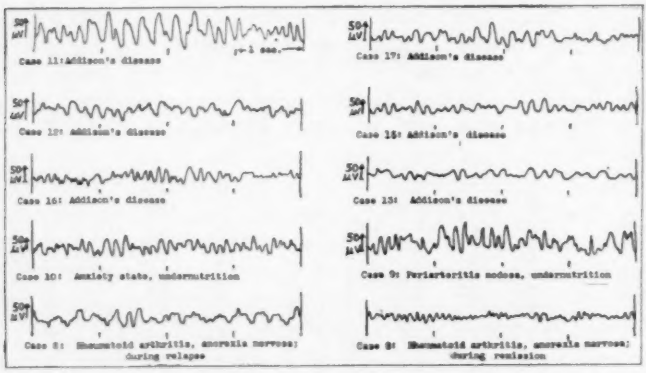
Case 11: Addison's disease
Case 17: Addison's disease
Case 12: Addison's disease
Case 18: Addison's disease
Case 16: Addison's disease
Case 13: Addison's disease
Case 10: Anxiety state, undernutrition
Case 9: Periarteritis nodosa, undernutrition
Case 8: Rheumatoid arthritis, anorexia nervosa; during relapse
Case 8: Rheumatoid arthritis, anorexia nervosa; during remission

Fig. 5.—Spontaneous electroencephalographic abnormalities in cases of defective carbohydrate metabolism.

has been designated as the "induction time." After completion of ninety to one hundred and twenty seconds of hyperventilation repeated bursts of these high potential waves continued for varying periods up to four and a half minutes. This has been called the "after discharge."

This hyperventilation effect was found to be closely correlated with the level of blood sugar. Figure 7 shows a typical condensed hyperventilation record taken before and thirty minutes after the ingestion of sugar. Suppression of the slow potentials is complete, even after one hundred and twenty seconds of hyperventilation. In some instances

18. Engel, G. L., and Margolin, S.: Clinical Correlation of the Electroencephalogram with Carbohydrate Metabolism, Arch. Neurol. & Psychiat. **45**:890 (May) 1941; Neuropsychiatric Disturbances in Addison's Disease and the Role of Impaired Carbohydrate Metabolism in Production of Abnormal Cerebral Function, ibid. **45**: 881 (May) 1941.

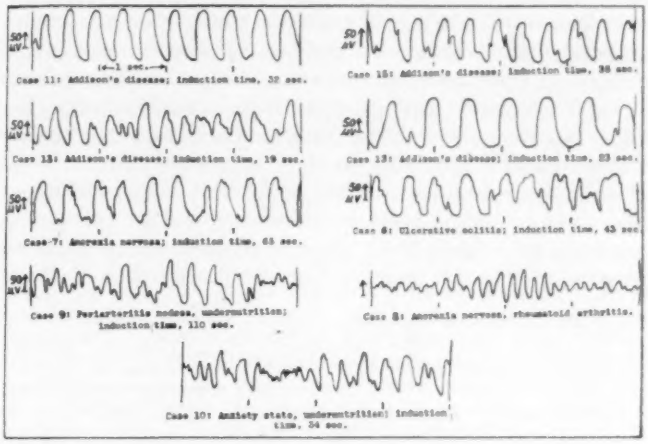
Case 11: Addison's disease; induction time, 32 sec.
Case 15: Addison's disease; induction time, 38 sec.
Case 12: Addison's disease; induction time, 19 sec.
Case 13: Addison's disease; induction time, 83 sec.
Case 7: Anorexia nervosa; induction time, 65 sec.
Case 6: Ulcerative colitis; induction time, 45 sec.
Case 9: Periarteritis nodosa, undernutrition; induction time, 110 sec.
Case 8: Anorexia nervosa, rheumatoid arthritis.
Case 10: Anxiety state, undernutrition; induction time, 54 sec.

Fig. 6.—Types of waves appearing in electroencephalograms on hyperventilation in cases of defective carbohydrate metabolism.

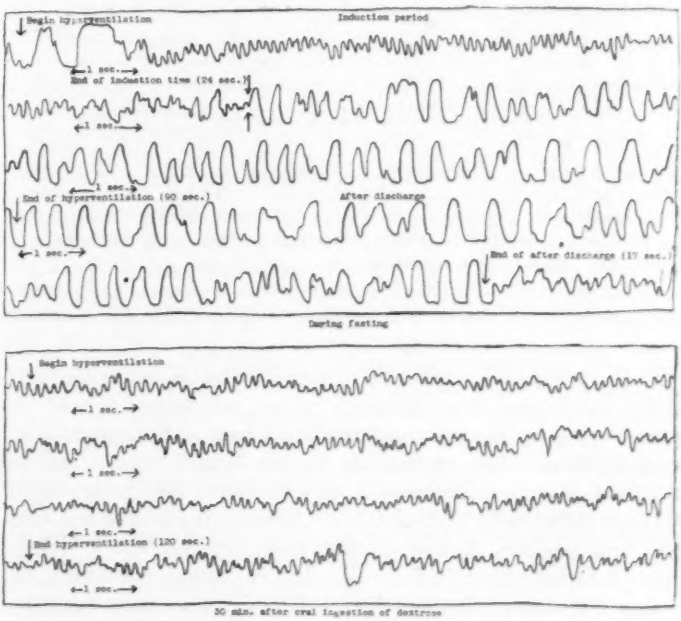
Induction period
End of induction time (24 sec.)
End of hyperventilation (90 sec.)
After discharge
End of after discharge (17 sec.)
During fasting
Begin hyperventilation
End hyperventilation (120 sec.)
30 min. after oral ingestion of dextrose

Fig. 7.—A typical hyperventilation record (condensed) in a case of Addison's disease before and thirty minutes after the ingestion of dextrose.

even four minutes of hyperventilation failed to bring out the slow waves after ingestion of sugar. When the amount of abnormal activity, expressed as the percentage of second intervals in the hyperventilation period containing 2 to 5 per second waves, was plotted against hourly levels of blood sugar, a close reciprocal relation was demonstrated (fig. 8, table 3). Similarly, the induction time, expressed in percentage of the hyperventilation time, paralleled the blood sugar curve. In other words, rising blood sugar decreased the amount of slow, high potential waves to the point of extinction, while the induction time was correspondingly increased. With a fall in blood sugar the reverse occurred. Dextrose appeared to protect the brain against the development of abnormal

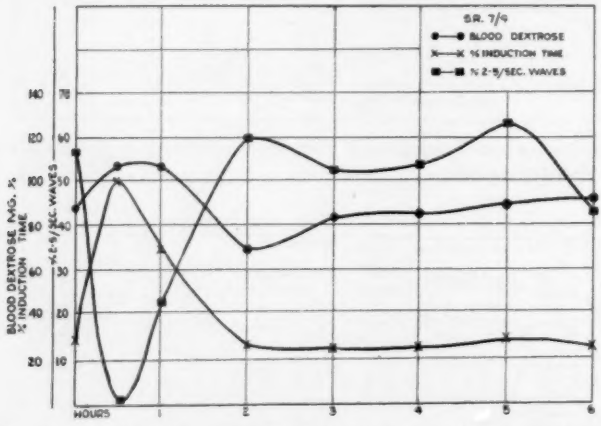

Fig. 8.—Relation between the level of blood sugar, the percentage of 2 to 5 per second waves and the percentage of induction time during a dextrose tolerance test in a patient with Addison's disease.

electrical activity. These observations were consistently checked in 11 experiments on 4 patients.

Toxic Deficiency States.—We observed 5 cases in which the patients had in common flat sugar tolerance curves, a tendency toward hypoglycemic reactions, neuropsychiatric disturbances and abnormal electroencephalograms. The underlying diseases varied widely, including 2 instances of anorexia nervosa, 1 with associated rheumatoid arthritis, and single instances of ulcerative colitis, periarteritis nodosa and anxiety state. All patients showed marked undernutrition and a relatively increased carbohydrate intake. No definite data are available as to the nature of the carbohydrate disturbance other than what might result from toxic, deficiency and nutritional factors.

In 2 cases (6 and 7) the patients had normal spontaneous electroencephalograms but showed marked hyperventilation effects identical

with those observed in cases of Addison's disease (figs. 6 and 7) except for slightly longer induction periods, ranging from forty-five to ninety seconds. After hyperventilation was discontinued, the abnormal slow potentials persisted for as long as ninety seconds. Abnormal potentials were abolished by dextrose and returned with falling blood sugar. In 1 case (6) four months after a complete recovery from active ulcerative colitis it was not possible to bring out any abnormal slow potentials, even after three minutes of hyperventilation in the fasting state. In the other case the patient showed no improvement clinically or electroencephalographically after two months of attempted therapy.

Case 6.—H. B., a 26 year old man with typical ulcerative colitis of several years' duration, was readmitted to the hospital because of recurrence of diarrhea and fever and loss of 60 pounds (27 Kg.) of weight. He weighed 104 pounds (47 Kg.) and appeared acutely and chronically ill, undernourished and dehydrated. The tongue was red and sore. Cheiloses were present. The abdomen was scaphoid and diffusely tender. A perirectal abscess was present. The patient had a fever which ran a hectic course, lost weight steadily and had intractable diarrhea.

The neurologic examination revealed nothing abnormal. The patient constantly whined, complained and demanded attention. He had periods of sudden panic and uncontrollable outbursts of tears. The mood was frequently inappropriate. On one occasion he had sudden loss of consciousness lasting ten minutes. The patient evinced an excessive desire for sweets, which predominated in his limited diet.

The standard dextrose tolerance curve was flat (table 3).

After surgical intervention the patient made a dramatic recovery. When seen four months later, he weighed 160 pounds (73 Kg.), felt well and exhibited none of the abnormal trends noted during his acute illness. The electroencephalogram was now entirely normal.

Case 7.—E. S., a 36 year old married white woman in a setting of emotional and domestic strain, experienced anorexia, nausea, vomiting, belching and episodes of epigastric pain, associated with loss of weight and strength. She became increasingly tense and irritable and had frequent crying spells. Menses became delayed.

On examination she appeared well developed but markedly undernourished and was complaining of abdominal distress. The blood pressure was 130 systolic and 90 diastolic. The abdomen was scaphoid and nontender. The pelvic examination revealed nothing abnormal.

Laboratory examination yielded the following data: hemoglobin concentration, 87 per cent; guaiac reaction of stool, negative; basal metabolic rate, —24 per cent; 15 mg. of urea nitrogen, 75 mg. of sugar, 540 mg. of cholesterol and 215 mg. of cholesterol ester per hundred cubic centimeters of blood, and dextrose tolerance curve, flat (table 3). Sigmoidoscopy and roentgen examination of the gastrointestinal tract revealed nothing abnormal.

The patient showed a great deal of anxiety and emotional lability and had crying spells and periods of agitation. She had frequent vague bodily complaints. Several episodes of extreme agitation, epigastric distress and sense of impending death responded promptly to a sweetened drink. The levels of blood sugar during these episodes ranged from 70 to 80 mg. per hundred cubic centimeters.

Attempts to improve the patient's nutrition were unsuccessful. It was felt that psychotherapy was indicated.

Comment: In this case the disturbed carbohydrate metabolism was secondary to the prolonged undernutrition. It appeared to increase the patient's abnormal trends and to make the development of insight into the nature of her gastrointestinal complaints more difficult.

In the 3 remaining cases the patients showed abnormalities in the electroencephalogram spontaneously and after hyperventilation. The hyperventilation effect was less striking in these cases. The spontaneous abnormalities again consisted of groups of slower (5 to 7 per second) waves. In 1 case (8) the patient had a marked remission of symptoms, during which the electroencephalogram became normal. With relapse the abnormal record again appeared (fig. 5).

CASE 8.—I. R., a 35 year old woman, experienced anorexia, weakness, pallor, loss of weight and amenorrhea fourteen months before admission, after serious emotional difficulties. Three months later psoriasis developed, followed by pain and stiffness of the joints and low grade fever. She had several admissions to other hospitals, where therapy was directed toward arthritis and anemia. Five months before entry she began to have episodes of weakness and faintness after fasts and had one convulsive episode. There was no past or family history of seizures. Her condition went gradually downhill, with a loss of 63 pounds (29 Kg.) of weight. Bronchopneumonia led to her final hospitalization.

The patient was markedly undernourished, cachectic and pale. Cheiloses were present, and the tongue and gums were red and sore. Numerous psoriatic patches were present. Most of the major joints, including those of the spine and phalanges, were stiff, painful, swollen and deformed. The blood pressure was 92 systolic and 68 diastolic. There were evidences of bronchopneumonia at the bases of both lungs. The abdomen was doughy. The neurologic examination revealed nothing abnormal.

The hemoglobin concentration was 72 per cent, and the blood contained 9 mg. of urea nitrogen, 70 mg. of sugar and 220 mg. of cholesterol per hundred cubic centimeters.

After a stormy course the patient recovered from the pneumonia. Severe involvement of the joints, fever, anorexia, weakness and faintness persisted. She frequently complained of dazed and unreal feelings, particularly before breakfast, and on one such occasion, she lost consciousness and convulsive movements developed. The level of blood sugar after the episode was 85 mg. per hundred cubic centimeters. The dextrose tolerance curve was flat (table 3). The electroencephalogram at this time showed the abnormalities illustrated in figures 5 and 6. The patient was markedly hyperirritable, emotionally labile, uncooperative and complaining and exhibited poor insight and judgment.

With the patient on a high calory, high vitamin diet and with spontaneous improvement in symptoms referable to the joints and a fall in temperature, appetite returned, episodes of morning weakness and faintness vanished and the general demeanor improved. The electroencephalogram was now entirely normal, before and after hyperventilation (figs. 5 and 6). The dextrose tolerance test showed some improvement (table 3).

Shortly after this the fever and symptoms referable to the joints recurred, and with them anorexia, weakness and the marked personality changes. The electroencephalogram again showed abnormal activity. The patient's course thereafter was progressively downhill, and she died four weeks later in collapse, after a generalized convulsion.

CASE 9.—E. G., a 19 year old girl, presented a one year history including rhinitis, asthma, diarrhea, pulmonary infiltrations, mononeuritides, eosinophilia, swelling of the joints and a maculopapulopurpuric eruption. Biopsy of affected skin confirmed the clinical diagnosis of periarteritis nodosa.

She was anorexic and extremely undernourished and showed marked emotional lability, with frequent weeping spells alternating with inappropriate hypomanic states and bursts of temper. Her family reported a change from her usual behavior.

The dextrose tolerance curve was flat (table 3). The electroencephalogram showed the abnormalities noted in figures 5 and 6. The hyperventilation effects vanished after the administration of sugar, remained in abeyance for two to three hours and then returned. The patient showed no improvement during the two and a half months of observation.

CASE 10.—P. D. was a 22 year old woman whose father had died of a massive hemoptysis. Eight months before admission she had a small hemoptysis, after which she became extremely upset and had frequent headaches, nervousness, weakness, vertigo, anorexia, palpitation and fatigue. Another hemoptysis led to her admission.

On examination she was tense and undernourished and was perspiring moderately. The blood pressure was 110 systolic and 80 diastolic. The remainder of the examination revealed nothing abnormal.

Extensive examination failed to reveal any cause for the hemoptysis, which was thought to be of benign bronchial origin.

A dextrose tolerance test yielded a flat curve, with a fall to 40 mg. per hundred cubic centimeters at three hours (table 3). The electroencephalogram showed bursts of 6 to 7 per second potentials and a shifting alpha frequency ranging from 8 to 12 per second. Hyperventilation produced bursts of 3 per second waves which disappeared for three hours after the ingestion of dextrose.

Comment on cases of abnormal carbohydrate metabolism: In this group of 13 cases we have attempted to demonstrate a relation between the neuropsychiatric symptoms and the altered carbohydrate metabolism. The electroencephalogram was used as an indicator of altered cerebral function. Two types of electrical abnormality were observed. First, there were spontaneous bursts of slow (2 to 6 per second) potentials, often of high voltage and originating diffusely from all portions of the cortex. These waves were only slightly influenced by changes in the level of blood sugar except during obvious hypoglycemic reactions, but they were unquestionably modified, to complete disappearance in some instances, by factors which effectively improved the carbohydrate metabolism, such as adequate replacement therapy in cases of Addison's disease or remission of the underlying disease in the other cases. An improvement in the dextrose tolerance curve always accompanied such clinical improvement. Secondly, the electroencephalograms in many cases showed an unusual sensitivity to the effects of hyperventilation. The sustained bursts of regular, high potential, slow waves, such as are illustrated, appeared after brief periods of overbreathing and persisted for long periods after overbreathing had been discontinued. This sensi-

tivity was markedly reduced by raising the blood sugar and in 1 instance, at least, disappeared completely when the underlying disease (ulcerative colitis) was cured. Whether this increased sensitivity to hyperventilation was due to a defect in the cerebrovascular mechanism which normally compensates for decreased carbon dioxide in the blood [19] or to a lowered threshold of cerebral reaction was not determined in this study, but it was unquestionably outside the normal range for the age group under consideration. The exceptionally high incidence of this phenomenon (5 out of 6) in a single group, such as the cases of Addison's disease, eliminated the possibility of mere coincidence. Further study of the incidence and mechanism of this phenomenon among various age groups will be necessary, however, before its clinical significance can be determined.

It is important to emphasize that the defect in carbohydrate metabolism in these cases involved more than simple hypoglycemia. Symptoms and electroencephalographic abnormalities were often present at relatively normal levels of blood sugar. When typical hypoglycemic reactions did occur, the level of blood sugar was usually higher than one ordinarily sees during induced insulin reactions in normal subjects. This also suggests a lowered threshold of cerebral reaction, possibly due to inefficient utilization of the available sugar by the central nervous system.

CONCLUSIONS

A series of cases has been presented in which clinical, metabolic and electroencephalographic data have been correlated. The results appear to warrant the conclusion that the varied neurologic and psychiatric manifestations observed could be attributed, on the one hand, to interference with the oxygen supply to the brain and, on the other, to inadequate carbohydrate utilization by the brain. The response to therapy directed toward correction of the underlying metabolic defect in several of these cases suggests the possibility of a more rational approach to the treatment of neurologic and psychiatric complications occurring in certain internal diseases. The value of the electroencephalograph in identifying this type of disturbance is clearly demonstrated and definitely suggests a more extensive use for this instrument in internal medicine.

SUMMARY

The requirements of the central nervous system for readily available oxygen and dextrose to maintain normal function form the basis for a report of a series of cases of generalized disease, in which neuro-

19. Lennox, W. G.; Gibbs, F. A., and Gibbs, E. L.: The Relationship in Man of Cerebral Activity to Blood Flow and to Blood Constituents, A. Research Nerv. & Ment. Dis., Proc. (1937) **18**:277, 1938.

psychiatric symptoms were ascribable to disturbances in these factors. The electroencephalogram was used as an indicator of altered cerebral metabolism.

The effects of acute cerebral anemia were studied in 30 cases of hypersensitive carotid sinus reflex. In 22 cases the patients complained of episodes of weakness, dizziness, faintness or syncope, and in 8 they exhibited symptoms suggestive of focal disease of the central nervous system. In all cases the spontaneous symptoms were reproduced by stimulation of the carotid sinus and were accompanied by bursts of 3 to 6 per second waves in the electroencephalogram. Blocking the vagal response with atropine in the first group abolished the symptoms and electroencephalographic changes but was without influence in the second group.

Acute cerebral anoxemia was demonstrated in a case of congenital heart disease in which any cardioaccelerator stimulus resulted in marked tachycardia, dyspnea, cyanosis, faintness, syncope and convulsions. A simultaneous electroencephalogram yielded slow, irregular, high potential waves during the neurologic reaction produced by slight exertion.

Four cases of chronic cerebral anoxemia due to markedly impaired respiratory exchange in long-standing asthma, bronchitis and emphysema are presented. The progressive development of neuropsychiatric signs was accompanied by increased slowing and irregularity of the electroencephalogram.

The effects of disturbed carbohydrate metabolism were studied in 8 cases of Addison's disease and 5 cases of secondary toxic and deficiency factors. In all of these cases the patients showed a variety of neuropsychiatric manifestations, flat sugar tolerance curves, abnormal carbohydrate appetites and electroencephalographic changes. The last consisted of an unusual sensitivity to the effects of hyperventilation which was greatly influenced by changes in the level of blood sugar and of spontaneous bursts of abnormally slow waves. All the electroencephalographic changes appeared to be modifiable by factors which improved carbohydrate metabolism, such as adequate replacement therapy in cases of Addison's disease and remission or cure in the other cases. Clinical improvement went hand in hand with changes in carbohydrate metabolism and in the electroencephalogram.

The therapeutic implications of these observations are discussed.

Dr. Hans Strauss, electroencephalographer to the hospital, gave advice and aid in the interpretation of the electroencephalograms.

Cincinnati General Hospital.
Mount Sinai Hospital.

VASCULAR PHASE OF CHRONIC DIFFUSE GLOMERULONEPHRITIS

A CLINICOPATHOLOGIC STUDY

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The term "accelerated" arteriosclerosis was first suggested by Löhlein [1] to designate those vascular changes which differentiated the benign from the malignant form of nephrosclerosis. The concept of acceleration of the arteriosclerotic process was later supported by Klemperer and Otani.[2] The characteristic arterial alterations which they emphasized consisted of cellular proliferation of the intima of the larger interlobular and arcuate arteries with associated narrowing of the lumen and coexistent necrosis of the arteriolar walls. Since these investigators were also able to demonstrate the usual arteriosclerotic process of elastica lamellation, intimal fibrosis and arteriolar hyalinization, they expressed the opinion that the addition of cellular intimal proliferations and necrotizing lesions evidenced a more rapid, or "accelerated," development of arteriosclerosis. The acute vascular alterations were ascribed to an ischemic mechanism incident to the accelerated arteriosclerotic changes in the medium-sized arteries and were considered to be degenerative rather than inflammatory in nature.

It was also suggested that "accelerated" arteriosclerosis was not peculiar to essential hypertension alone but also appeared in renal diseases other than the primarily vascular variety. It was stated to occur notably in chronic diffuse glomerulonephritis, and the view was expressed by Klemperer and Otani [2] that in this condition, as in essential hypertension, the accelerated type of vascular lesion probably was of a similar

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From the Medical Services and Laboratories of Mount Sinai Hospital.

Presented in part at the Graduate Fortnight of the New York Academy of Medicine, "Medical and Surgical Disorders of the Urinary Tract," Nov. 1-12, 1937.

1. Löhlein, M.: Zur Pathogenese der vascularen Schrumpfniere, Med. Klin. **12**:741, 1916; Ueber Schrumpfnieren, Beitr. z. path. Anat. u. z. allg. Path. **63**:570, 1917.

2. Klemperer, P., and Otani, S.: Malignant Nephrosclerosis (Fahr), Arch. Path. **11**:60 (Jan.) 1931.

morphogenesis. The inference further was drawn that in instances of chronic diffuse glomerulonephritis in which there was histologic evidence of "accelerated" arteriosclerosis a rapid tempo was exhibited clinically and therein the condition resembled malignant nephrosclerosis.

Fishberg [3] had previously called attention to the frequent occurrence of severe arteriosclerotic and arteriolonecrotic lesions in cases of chronic diffuse glomerulonephritis and expressed the opinion that such lesions were the result of hypertension. Kimmelstiel and Wilson [4] also noted the presence of "endarteritic" and arteriolonecrotic lesions in patients with chronic glomerulonephritis who had had severe hypertension. More recently Wagener and Keith [5] reported the coexistence of chronic diffuse glomerulonephritis and diffuse arteriolar disease and stated:

> At present, the exact relationship between the two pathologic processes is unknown, and it is obvious that there is much still to learn regarding the etiology and development of the two conditions.

Baehr [6] and Wilson [7] have similarly alluded to the occurrence of advanced "malignant" arterial lesions in patients with chronic nephritis who exhibited severe hypertension, while especial emphasis was laid on the clinical resemblances of the conditions of these patients to malignant nephrosclerosis. The association of chronic diffuse glomerulonephritis and a clinical picture of malignant hypertension has been more recently reiterated by Derow and Altschule.[8]

The common appearance of the syndrome of "malignant" hypertension in cases of chronic diffuse glomerulonephritis has suggested that the morphologic substratum of the clinical resemblances may reside in the vascular lesions which are common to both morbid processes. It is the purpose of this report to present the results of a correlative study of this question.

MATERIAL AND METHOD

The material studied comprises 49 consecutive cases of chronic diffuse glomerulonephritis selected over twelve years (Jan. 1, 1927 to July 1, 1938) from a total of 5,232 autopsies. Specimens were fixed in a 4% per cent solution of formaldehyde U. S. P., Kaiserling I solution or Jores solution. Sections of the kidneys, pancreas,

3. Fishberg, A. M.: The Arteriolar Lesions of Glomerulonephritis, Arch. Int. Med. **40**:80 (July) 1927.

4. Kimmelstiel, P., and Wilson, C.: Benign and Malignant Hypertension and Nephrosclerosis, Am. J. Path. **12**:45, 1936.

5. Wagener, H. P., and Keith, N. M.: Diffuse Arteriolar Disease with Hypertension and the Associated Retinal Lesions, Medicine **18**:317, 1939.

6. Baehr, G.: Clinical Pathological Conferences, Mount Sinai Hospital, J. Mt. Sinai Hosp. **3**:53, 1926; **5**:158, 1938.

7. Wilson, C., cited by Wilson, C., and Pickering, G. W.: Acute Arterial Lesions in Rabbits with Experimental Renal Hypertension, Clin. Sc. **3**:343, 1938.

8. Derow, H. A., and Altschule, M. O.: The Nature of Malignant Hypertension, Ann. Int. Med. **14**:1768, 1941.

adrenals, testes and myocardium in particular and all other available organs in addition were diligently examined. The sections were all embedded in paraffin and routinely stained with hematoxylin and eosin. The Weigert elastica-Van Gieson combination, the McGregor modification of the Mallory-Heidenhain and congo red stains were used where indicated.

In order to assure a purely objective evaluation of the histologic material, the study of the clinical aspects of the cases was postponed until the interpretation of morphologic data had been formulated. On the basis of the vascular picture a designation of either "slowly progressive" or "accelerated" type of arteriosclerosis was made. The criteria employed for the designation "advanced accelerated" form was extreme narrowing of the interlobular arteries produced by cellular intimal proliferation associated with necrosis of arterioles. In those instances of the accelerated type in which cellular intimal arterial proliferations were observed but arteriolonecrosis was absent the condition was termed "transitional." In the slowly progressive disease the changes included intimal thickening, fatty change, elastosis and arteriolar hyalinization.

A review of the clinical records was then made entirely separately. In each case the condition was similarly designated slowly progressive or accelerated ("malignant") on the basis of the height of hypertension and the presence or absence of neuroretinopathy. The anatomic and clinical data were then assembled and correlated (table 1).

A preliminary study was made not only of routine cases of acute and subacute diffuse glomerulonephritis but of various types of inflammatory processes, in order to ascertain the relation of inflammation to the vascular tree and to compare the arteriopathies with those observed in cases of the chronic phase of glomerulonephritis.

Deserving of special mention are the occasional cases in which differentiation between chronic diffuse glomerulonephritis and malignant nephrosclerosis was difficult due to widespread arterial changes. The extent of damage to the glomerular tufts and parenchyma and the age of the process constituted the basis for the final diagnosis. Wherever extensive active glomerular damage, replacement fibrosis and atrophy were observed, it was assumed that we were dealing with primary inflammatory glomerular disease. This belief was fortified by examining contracted benignly nephrosclerotic kidneys. In these, despite widespread vascular and glomerular involvement, the glomerular tufts still disclosed comparatively lesser changes than those in the nephritic group, while inflammatory lesions were absent. In cases of the malignant variety of essential hypertension active degenerative, inflammatory and proliferative glomerular lesions were observed, but these were usually isolated. To be sure, fibrotic loops or tufts were also encountered in cases of malignant nephrosclerosis, but these were of a more patchy character than those observed in cases of chronic diffuse glomerulonephritis. Criticism may be applied by the reader on the assumption that instances of malignant nephrosclerosis have been inadvertently included in our accelerated group. This possibility has been assiduously considered but, we believe, completely eliminated. All cases included in this study were considered to be unequivocal examples of diffuse glomerulonephritis.

REPORTS OF THREE ILLUSTRATIVE CASES

SLOWLY PROGRESSIVE TYPE

CASE 9.—S. G., a white female aged 44, entered Mount Sinai Hospital because of increasing weakness and malaise of three years' duration. Fourteen years previously she had had a spontaneous abortion. She had been well until the onset

Case No.	Age, Yr.	Sex	Urea Nitrogen, Mg. per 100 Cc.	Cardiac Failure	Neuro-retino-pathy	Blood Pressure, Mm. Hg		Weight of Kidneys, Gm.		Slowly Progressive Arteriosclerosis		Accelerated Arteriosclerosis		Arteriolonecrosis	
						Systolic	Diastolic	Right	Left	Kidneys	Other Organs	Kidneys	Other Organs	Kidneys	Other Organs
Slowly Progressive Arteriosclerosis															
1	36	M	135	+	0	160	100	120	110	++	++	0	0	0	0
2	33	M	82	—	0	126	90	130	130	+	+	0	0	0	0
3	24	M	243	+	0	163	104	60	60	+++	+	0	0	0	0
4	33	F	117	+	0	140	98	50	75	+++	+	0	0	0	0
5	24	M	260	—	0	150	96	Atrophic		+++	+	0	0	0	0
6	33	F	112	—	0	180	104	60	70	+++	+	0	0	0	0
7	22	F	68	+	0	134	80	Atrophic		++	+	0	0	0	0
8	15	M	238	+	0	100	60	70	80	Slight	0	0	0	0	0
9	44	F	120	—	0	175	100	75	75	++	0	0	0	0	0
10	31	M	102	+	0	152	88	150	150	++	++	0	0	0	0
11	52	F	150	—	0	128	78	80	85	++	+	0	0	0	0
12	42	F	144	—	0	140	74	105	120	+	+	0	0	0	0
13	2	M	90	—	No examination	138	100	...	...	+	0	0	0	0	0
14	53	M	152	+	0	210	100	130	140	+++	Slight	0	0	0	0
Transitional Accelerated Arteriosclerosis															
15	24	M	80	—	2	180	110	80	80	+++	+	+	0	0	0
16	30	F	158	—	0	192	130	50	120	++	+ to ++	Left, 0; right, +	0	0	0
17	22	F	126	—	1	218	134	45	50	++	++	++	0	0	0
18	23	F	181	+	2	208	92	..	70	++	Slight	+	0	0	0
19	13	F	195	—	2	140	100	70	60	+	0	++	0	0	0
20	18	M	180	—	0	152	102	60	60	++	++	+	0	0	0
21	41	F	145	+	0	220	120	85	100	+++	+	+	0	0	0
22	21	M	88	+	No examination	195	130	160	160	++	++	Occasionally slight	0	0	0
23	48	M	138	+	No examination	210	110	110	110	++	++	+	0	0	0
24	54	M	85	+	2	225	112	200	200	+++	++	+	0	0	0
25	36	F	153	+	1	280	74	50	60	++	+	+	0	0	0
26	30	F	185	+	2	230	120	70	60	++++	++	++	0	0	0
27	21	M	104	+	1	160	100	125	135	+	+	+	0	0	0
Advanced Accelerated Arteriosclerosis															
28	35	F	76	+	1	224	120	70	50	++	+++	+	+	++	0
29	24	M	160	—	1	190	44	100	125	+++	+	++	0	+	0
30	22	F	184	—	1	170	120	75	75	+++	+	++	0	+	0
31	28	F	131	+	2	220	180	50	60	++++	+	+	0	+	0
32	45	M	131	+	1	200	110	110	110	+++	++	+	Slight	+	0
33	27	M	120	+	2	216	152	110	110	++	++	++	+	+	0
34	33	M	111	—	2	220	130	100	95	++	Slight	+	0	+	0
35	37	F	154	+	1	224	110	130	120	++	Slight	++	0	++	+
36	37	M	230	—	1	150	110	80	110	+++	+++	+	0	+	+
37	20	F	118	+	2	200	140	75	75	++	+	Slight	0	+	0
38	42	M	120	+	1	180	96	115	130	++	+	+	0	+	0
39	48	M	110	+	1	214	136	100	100	+++	+	++	0	+	0
40	21	M	228	+	2	220	140	110	95	+	++	+	0	+	0
41	30	M	153	+	2	216	126	40	40	+	0	+	0	+	0
42	28	F	142	+	1	230	160	125	125	+++	+++	++	+	+	0
43	29	F	118	+	2	170	100	125	100	++	+	++	0	+	0
44	32	M	63	+	1	210	130	140	130	+++	+	++	0	++	0
45	23	M	212	+	2	180	115	90	85	+++	++	++	0	+	0
46	34	M	102	+	1	230	140	100	100	+++	+++	++	0	++	+
47	24	M	195	—	1	220	130	120	130	++	++	+	+	+	+
48	25	M	124	—	2	246	160	75	Atrophic	++	++	+	0	++	+++
49	22	M	109	+	2	220	140	110	100	++	++	+	0	++	+++

* The following figures have been employed with reference to the condition of the eyegrounds; 0, normal optic disks; 1, blurring of disk margins, and 2, measurable swelling of the nerve heads. Elsewhere in the table 0 signifies normal condition of an organ.

of her present complaints, when hypertension and albuminuria were first discovered. Postexertional dyspnea and palpitation soon became evident, while one year prior to her admission to the hospital she had begun to lose weight and to complain of generalized aches and pains. At that time she was examined in the outpatient department, where moderate albuminuria, inability to concentrate the urine above 1.010, a systolic blood pressure of 180 mm. of mercury, a diastolic pressure of 106 mm., a hemoglobin concentration of 54 per cent and a blood urea nitrogen content of 76 mg. per hundred cubic centimeters were observed. Two nights before hospitalization she had a bout of hemoptysis.

Physical Examination.—The patient was pallid and lethargic and her breath had a uriniferous odor. Examination of the fundi revealed tortuous arteries; the optic disks showed no abnormalities. Numerous coarse rales were audible over the entire lower lobe of the right lung, and occasional rales were heard over the right side of the chest anteriorly. A systolic murmur was audible at the base of the heart, coarse over the pulmonic area and transmitted into the neck. The second aortic sound was greater than the second pulmonic sound. The cardiac rhythm was regular, with a rate of 100 per minute. There was no peripheral edema. The radial arteries were moderately sclerotic. The blood pressure was 175 systolic and 100 diastolic measured in millimeters of mercury.

Laboratory Data.—The hemoglobin concentration was 52 per cent (Sahli); the red cells numbered 2,850,000, and the white cells, 6,000 per cubic millimeter, with 71 per cent polymorphonuclear leukocytes. The Wassermann reaction of the blood was negative. A teleroentgenogram disclosed moderate enlargement of the heart both to the right and to the left. An electrocardiogram revealed low voltage and a tendency to left axis deviation. Urinalysis revealed a specific gravity varying between 1.008 and 1.014 and a positive reaction for albumin (2 plus), and occasional erythrocytes and casts were seen in the urinary sediment. The blood contained per hundred cubic centimeters an average of 120 mg. of urea nitrogen, 290 mg. of cholesterol, 8.0 mg. of creatinine and 525 mg. of chlorides. The carbon dioxide–combining power was 41 volumes per cent.

Course of Illness.—Despite the administration of intravenous fluids and supportive therapy, the patient died two weeks after her admission.

Necropsy.—The diagnoses included chronic diffuse glomerulonephritis with moderate contraction of the kidneys, hypertrophy and dilatation of the heart, early fibrinous pericarditis and pulmonary and cerebral edema. On gross examination the kidneys weighed 150 Gm. together and were normal in shape and moderately firm. The capsules were stripped with difficulty and revealed a finely granular surface with scattered hemorrhagic foci. The cut surfaces showed a pale brownish red, narrowed cortex through which irregular grayish yellow streaks were scattered. The corticomedullary demarcation was indistinct. The renal vasculature showed no significant gross abnormalities. The pelves and ureters and the urinary bladder presented no changes. Microscopic examination of the kidneys revealed widespread glomerular fibrosis, frequent adherence to the capsular epithelium and severe atrophy of the glomerular tufts. Glomerular ischemia was striking. Focal epithelial proliferation and an occasional increase in polymorphonuclear leukocytes were noted. The interstitial connective tissue was markedly increased. The renal vascular tree revealed slight to moderate elastic reduplication of the medium-sized or larger arteries with associated intimal thickening and narrowing of the lumens. There was moderate arteriolar thickening and early hyalinization. The tubules

were frequently dilated and contained granular and hyaline material, epithelial cells and leukocytes. The tubular cytoplasm was often granular, and a fair number of nuclei disclosed degenerative phenomena.

ACCELERATED TYPE

Transitional Form.—CASE 21.—S. L., a 41 year old housewife with known renal disease of twenty-two years' duration, entered Mount Sinai Hospital in the service of Dr. George Baehr on March 27, 1933 with a history of vomiting, weakness and pallor of two months' duration. She also complained of palpitation, urinary frequency and visual disturbances. Five days previously, a sore throat had developed and she had experienced considerable difficulty in swallowing. At this time her physician found enormously swollen tonsillar pillars. Three days later she expectorated small amounts of blood. On the day of hospitalization she again visited her physician, who discovered marked drowsiness and muscular twitchings. Her blood pressure was then 220 systolic and 120 diastolic, measured in millimeters of mercury. While she was in the physician's office she had a convulsion and then lapsed into coma. Phlebotomy reduced her blood pressure to 160 mm. of mercury systolic and 100 mm. diastolic.

Physical Examination: The patient was moribund, and her breath had a uriniferous odor. Examination of the fundi revealed the margins of the optic disks to be sharp; the vessels were greatly narrowed and irregular, and few hemorrhages and some exudate were present. The heart was conspicuously enlarged. The cardiac rhythm was wholly irregular. The ventricular rate was 160 and the pulse rate 132 per minute. The second aortic sound was greater than the second pulmonic sound. The edge of the liver was palpable 2 fingerbreadths below the costal margin. Slight edema of the lower extremities was present. The blood pressure was now 180 mm. of mercury systolic and 120 mm. diastolic.

Laboratory Data: The hemoglobin concentration was 55 per cent (Sahli), and the white cell count, 9,100 per cubic millimeter, with 95 per cent polymorphonuclear leukocytes. Urinalysis revealed a specific gravity of 1.008 and a positive reaction for albumin (3 plus), and occasional red cells and frequent white cells were seen in the sediment. The blood contained 145 mg. of nitrogen and 170 mg. of sugar per hundred cubic centimeters. The carbon dioxide–combining power was 26.5 volumes per cent.

Course of Illness: The patient suffered a convulsion shortly after admission. Accordingly, a lumbar tap was performed, which showed a slightly increased spinal fluid pressure. The tap was soon followed by another convulsion and death.

Necropsy: The diagnoses included chronic diffuse glomerulonephritis with moderate contraction of the kidneys, hypertrophy and dilatation of all chambers of the heart, acute fibrinous pericarditis, pulmonary edema, chronic passive congestion of the lungs and the liver and bronchopneumonia of the lower lobes of the lungs. Death was attributed to the association of renal and of cardiac failure. On gross examination the kidneys were small; the right one weighed 85 Gm., and the left one, 100 Gm. The capsules were stripped with considerable difficulty, leaving a pale gray, finely granular surface. The granules were pinhead to split pea in size, and the intervening tissue was smooth and slightly depressed. On section the cortex was diminished in width, and the basic markings were absent; the corticomedullary demarcation was indistinct. Microscopic examination of the kidneys revealed widespread partial to complete replacement fibrosis, atrophy and focal and confluent hyalinization of the malpighian bodies. A fair number were conspicuously enlarged, contained increased numbers of epithelial and endothelial cells and were irregularly

adherent to the capsular epithelium. The interstitium was irregularly increased and was the site of small round cells, plasma cells and fibroblasts. There was a moderate degree of collar-like alteration around the bodies; their lumens were commonly distorted, occasionally dilated and showing cellular multiplication, but more frequently compressed with cellular atrophy. The lumens contained epithelial, red and rarely white cells and albuminous and hyaline material. Peritubular hyalinization and marked capillary engorgement were noted. There was also evidence of associated acute and subacute pyelonephritis. Cellular and edematous thickening of the larger, medium-sized and smaller interlobular arteries with occasional severe narrowing of the lumens was striking. Scattered mural calcification of the medium-sized arteries was noted. Occasional medial hypertrophy, hyalinization of the arteriolar walls and fibrotic intimal thickening of the larger arteries were also encountered. No necrotic vascular lesions were present.

Advanced Form.—CASE 33.—First Admission: R. K., a 27 year old Hungarian clerk, had been well until six years prior to his admission to Mount Sinai Hospital in the service of Dr. B. S. Oppenheimer on May 11, 1931, when he first noticed edema of both legs. He was then hospitalized at another institution, where a diagnosis of acute diffuse glomerular nephritis was made. At that time the blood contained 20 mg. of urea nitrogen per hundred cubic centimeters. He was discharged improved after sixteen days and remained asymptomatic for six years. Four weeks before his admission to Mount Sinai Hospital, his ankles and legs again began to swell and he complained of marked weakness and oliguria. Six days previously he had noted hematuria.

Physical examination: The patient had a pasty complexion and a puffy face. The optic nerve heads were of good color; the margins were slightly serrated. The retinal arteries showed a high light reflex and evidence of perivasculitis. The neck veins were full. Dulness was elicited at the bases of both lungs. There was no clinical evidence of cardiac enlargement or no cardiac murmurs. The second pulmonic sound was greater than the second aortic sound. A fluid wave was elicited in the abdomen, and pitting edema was present over the ankles and the trunk. The blood pressure was 200 systolic and 110 diastolic, measured in millimeters of mercury.

Laboratory data: The hemoglobin concentration was 65 per cent (Sahli). The white cells numbered 6,400 per cubic millimeter, with 80 per cent polymorphonuclear leukocytes. Urinalysis revealed a specific gravity not exceeding 1.012 and a positive reaction for albumin (4 plus); many erythrocytes and occasional casts were seen in the sediment. The result of the Esbach determination was 7 Gm. daily. The blood contained per hundred cubic centimeters 66 mg. of urea nitrogen, 270 mg. of cholesterol, 7.2 mg. of calcium, 3.7 mg. of phosphorus and 4.1 Gm. of total protein, with 2.3 Gm. of albumin and 1.8 Gm. of globulin. The carbon dioxide–combining power was 41 volumes per cent. An electrocardiogram showed changes suggestive of left ventricular preponderance; a teleroentgenogram showed an enlarged heart. The diagnosis was chronic diffuse glomerulonephritis in an early nephrotic phase.

Course of illness: The patient was treated with dietary means and injections of mercurials. He was discharged six weeks after this admission, at which time the urea nitrogen in the blood had fallen to 38 mg. per hundred cubic centimeters. Erythrocytes were no longer seen in the urinary sediment, and the result of the Esbach determination fell to 2 Gm. for twenty-four hours. The edema of the ankles was then minimal.

Second Admission: The patient was readmitted seven months later because of blurred vision, headaches, expectoration of rusty sputum, vomiting and loss of

20 pounds (9 Kg.) in weight. Two months prior to readmission he was seen at the follow-up clinic, where blurring of the margins of the optic disks was noted. Evidence of moderate cardiac failure was present. His blood pressure at that time was 170 systolic and 110 diastolic, measured in millimeters of mercury. On admission to the hospital his blood pressure was 230 systolic and 120 diastolic. The optic nerve heads were now edematous, and their margins, blurred and hyperemic. The retinal arteries were thin and of irregular caliber. A large amount of exudate was present. There were a star-shaped figure at the macula and zones of fibrinous exudate about the nerve heads. Auscultation of the chest disclosed a gallop cardiac rhythm and rales throughout the lungs. There was slight pretibial edema.

Laboratory data: The urine concentration test showed a maximum concentration to 1.012. The reaction for albumin was positive (2 plus). Neither casts nor erythrocytes were found in the sediment. The blood contained per hundred cubic centimeters 57 mg. of urea nitrogen, 4 mg. of creatinine, 7.4 mg. of calcium, 4.4 mg. of phosphorus, 340 mg. of cholesterol and 5.5 Gm. of total protein. An electrocardiogram again showed deviation of the electrical axis to the left, and the T wave in lead II was partially inverted. A teleroentgenogram revealed evidence of dilatation of both ventricles. The patient remained in the hospital for seven days, with little change in his condition, and left the hospital against advice.

Third Admission: Two months later the patient again sought admission because of severe epistaxis. The previous symptoms had become progressively worse.

Physical examination: The optic nerve heads and margins of the optic disks were obscured. There was slight peripapillary edema (1 D.). The edge of the liver was palpable at the level of the umbilicus, and both legs were edematous. The blood pressure was 216 systolic and 152 diastolic, measured in millimeters of mercury.

Laboratory data: The specific gravity of the urine was 1.010. Albuminuria and cylindruria were present.

Course of illness: The blood contained 68 mg. of urea nitrogen per hundred cubic centimeters, but the level rose progressively in ten days to 120 mg. per hundred cubic centimeters. The daily urinary output fell to 300 cc. Treatment of cardiac failure was of no avail, and the patient died with the typical manifestations of uremia (urea frost, muscular twitchings and a pericardial friction rub).

Necropsy: The diagnoses included chronic diffuse glomerulonephritis with vascular necrosis, marked fibrinous pericarditis, hypertrophy and dilatation of left cardiac and right ventricular chambers, coronary arteriosclerosis with moderate narrowing of the lumens, chronic passive congestion of all viscera and anasarca. Death was due to the association of renal and of cardiac failure. On gross examination each kidney weighed 110 Gm. and was firm in consistency. The capsules stripped with moderate ease, revealing a diffusely granular, reddish gray surface with scattered, discrete, pinhead-sized hemorrhages. The granules varied from 1 to 2 mm. in diameter and were enclosed by depressed reddish gray zones. The sectioned surfaces disclosed sharp corticomedullary delineation. The pelves and ureters and the urinary bladder were the seat of a few submucosal hemorrhages. On histologic examination there was a paucity of glomeruli. The majority showed various stages of fibrosis, atrophy and hyalinization, while scattered tufts revealed increased cellularity with predominant epithelial cell proliferation and here and there hyperplasia of the capsular epithelium with suggestive early crescent formation. Adhesion between the tufts and capsule, interstitial fibrosis with conspicuous infiltration with lymphocytes and scattered foci of hemorrhage were noted. The tubular epithelium showed degenerative alterations, including fatty change, nuclear pyknosis and irregularly alternating dilatation and compression of

the lumens. The lumens frequently contained abundant numbers of erythrocytes, eosinophilic debris and desquamated epithelial cells. In addition to intimal fibrosis, elastosis and arteriohyalinization, there were cellular and edematous intimal thickening of the medium-sized arteries, fatty change, "hyaline" thrombi of arterioles, scattered arteriolonecrosis and impregnation of their walls with erythrocytes. Of the other organs only the pancreas and adrenals showed any significant vascular alterations. These consisted of "foamy" and cellular intimal thickening with associated narrowing of the lumen, arteriohyalinization of the pancreatic arteries and hyaline intimal degeneration of scattered adrenal arterioles.

CLINICAL FINDINGS (Table 1)

A preponderant number of males were affected in the advanced accelerated group, while the remaining groups showed no significant sex variations. The age range extended from 2 to 60 years. The average duration of the clinical picture of glomerulonephritis was approximately similar in all groups, although the exact onset of the

TABLE 2.—*Range of Blood Pressure in Forty-Nine Cases of Chronic Diffuse Glomerulonephritis*

Type of Arteriosclerosis	Systolic Pressure		Diastolic Pressure	
	200 Mm. Hg or Over, %	Below 160 Mm. Hg %	120 Mm. Hg or Over, %	100 Mm. Hg or Over, %
Slowly progressive	7 (1 case)	80	0	36
Accelerated				
Transitional	54	16	38	84
Advanced	73	4 (1 case)	70	91

disease in several instances could not be accurately ascertained. However, with the appearance of severe hypertension the course of a patient's illness was more rapidly terminated.

Albumin, erythrocytes, all forms of casts and leukocytes in varying numbers were present in the urine in all cases. No correlation could be established between either the severity or the tempo of the clinical course and the character of the urinary sediment. Poor variability of the specific gravity of the urine and azotemia were found to be common to all cases. In the greater number death was attributable to uremia alone, while in some cases the association either of cardiac failure, an intercurrent infection or a surgical procedure was considered to be a responsible factor. Cardiac failure was found to be a more frequent complication in the accelerated group. In those cases in which definite cardiac insufficiency was present, it was believed to have either precipitated or intensified the uremic manifestations through the mechanism of prerenal fluid deviation.

The blood pressure in the three groups exhibited striking differences (tables 1 and 2). The systolic blood pressure in the slowly progressive group usually varied between 100 and 180 mm. of mercury. In 1

instance it was found to be 210 mm. In 80 per cent of the cases, however, it was below 160 mm. The diastolic blood pressure ranged between 60 and 104 mm., while in only 2 cases did it exceed 100 mm. It is worthy of emphasis that the blood pressure in 5 instances was normal despite the absence of cardiac failure. Similar observations of normal blood pressure in patients with glomerulonephritis have been reported by Jores [9] and others.[10]

In contrast to the systolic blood pressure in the slowly progressive group, that in the advanced accelerated group varied between 150 and 246 mm. of mercury. In 73 per cent of cases the systolic blood pressure was 200 mm. or higher, while in only 1 case was it below 160 mm. The diastolic blood pressure level in 91 per cent had been 100 mm. of mercury or higher, and in 70 per cent it had reached 120 mm. or more. In the transitional group the systolic blood pressure varied between 140 and 280 mm. of mercury. In 54 per cent of cases the systolic blood pressure had exceeded 200 mm. In 2 cases it was below 160 mm.; the patient in 1 case was a boy aged 13 and in the other an infant aged 2. In 84 per cent of the cases in the transitional group the diastolic blood pressure reached 100 mm. of mercury or over and in 38 per cent it was 120 mm. of mercury or higher. Thus a striking association of severe vascular lesions with marked hypertension was noted to exist.

The fundus oculi both in the advanced accelerated and in the transitional group showed conspicuous differences from that in the cases of slowly progressive disease, although narrow vessels and ones of irregular caliber, arteriovenous compression and retinal exudates were common to all cases included in this study. The optic disks were normal in every case in the slowly progressive group, while neuroretinopathy was observed in 96 per cent of the cases in the advanced accelerated group (tables 1 and 3). Papilledema was likewise noted in 62 per cent of the cases in the transitional group. It is significant that whereas normal optic disks were visualized in 3 cases during earlier periods of hospitalization, papilledema was seen to have appeared in the same cases during subsequent observations. In 2 other cases atrophy had replaced edema of the nerve head. Peripapillary retinal edema was present in 14 instances. In 1 case the optic disk of one eye was normal, while the other showed definite swelling, presumably consequent to unilateral vascular involvement. Detachment of the retina secondary to the underlying edema had occurred in 2 patients, while reattachment was observed

9. Jores, L.: Ueber die Beziehungen der Schrumpfnieren zur Herzhypertrophie von pathologische Standpunkt, Deutsches Arch. f. klin. Med. **94**:1, 1908.

10. Foster, N. B.: The Relations of Hypertension to Cardiorenal Diseases, Am. J. M. Sc. **164**:808, 1922. Bannick, E. G.: Severe Chronic Glomerular Nephritis Without Hypertension, Cardiac Hypertrophy or Retinal Changes: Report of Two Cases, Arch. Int. Med. **39**:741 (May) 1927.

to have taken place in 1. In only 4 instances in the advanced accelerated and transitional groups were the optic nerve heads considered to be normal in appearance—1 in the former and 3 in the latter. In 3 cases the fundi were not described.

The color of the disks was definitely recorded in 13 of the 32 cases in which neuroretinopathy had been present. In 8 hyperemia of the disk was observed, while in 5 the nerve heads were pale. Thus, in our cases hyperemia of the disk was noted with greater frequency than was pallor.

These data are somewhat at variance with those reported by Keith and his co-workers,[11] who stressed pallor as characteristic of the disk in patients with glomerulonephritis and held this in contrast to hyperemia of the disk occurring in cases of malignant nephrosclerosis. They expressed the belief, in addition, that sclerosis of the retinal arterioles was absent in cases of chronic diffuse glomerulonephritis. In our series, however, retinal arteriosclerosis had been observed in almost every case.

TABLE 3.—*Incidence of Neuroretinopathy in Forty-Nine Cases of Chronic Diffuse Glomerulonephritis*

Type of Arteriosclerosis	Percentage of Cases
Slowly progressive	0
Accelerated	
Transitional	62
Advanced	96

A similar experience had been previously stated by Cannady and O'Hare.[12]

FACTORS CONCERNED IN OCCURRENCE OF OCULAR LESIONS

It appeared in this study that when severe hypertension had become definitely established, advanced neuroretinopathy either was coexistent or was soon to follow and, further, that it indicated the probable existence of accelerated visceral vascular lesions. The belief that the neuroretinopathic changes were the sequel of long-standing severe hypertension was substantiated further by their absence in the slowly progressive group and their development in those instances in which there had been a pronounced elevation of blood pressure. Moschcowitz[13] long ago intimated that such retinopathy is secondary to arterial lesions, which themselves represent the effects of a preexistent hypertension.

11. Keith, N. M.; Wagener, H. P., and Kernohan, J. W.: The Syndrome of Malignant Hypertension, Arch. Int. Med. **41**:141 (Feb.) 1928.

12. Cannady, E. W., and O'Hare, J. P.: A Critical Survey of the Retinal Lesions in Chronic Glomerular Nephritis, J. A. M. A. **103**:6 (July 7) 1934.

13. Moschcowitz, E.: Hypertension with Minimal Renal Lesions, J. A. M. A. **77**:1095 (Oct. 1) 1921.

The studies reported by Cannady and O'Hare [12] lend support to this belief. In the series of cases of chronic diffuse glomerulonephritis which they investigated, severe retinal lesions were noted in 25 of 32 cases. Hypertension was found to precede the appearance of retinal arteriolar change in 13 of the 17 cases in which these authors had observed the disease since its early stages. It is noteworthy that in 2 of their cases in which retinal lesions were absent hypertension was also not present.

The parallelism which existed between extreme hypertension and neuroretinitis in cases of chronic diffuse glomerulonephritis was fully recognized by Fishberg and Oppenheimer.[14] Of 45 patients with chronic diffuse glomerulonephritis, 17 exhibited neuroretinitis, and "all of these patients gave evidence of either present or past hypertension." After reviewing the evidence, Fishberg [15] subsequently concluded: "Hypertensive neuroretinopathy appears to be of the same pathogenesis in both essential hypertension and glomerulonephritis."

In view of the presence of azotemia in the cases presented here, such a fact may be judged erroneously to play a contributory role in the appearance of the neuroretinopathic picture. Several studies, however, deny importance to this contention. Behan [16] recorded the presence of neuroretinitis in patients with hypertension in whom evidence of renal impairment was absent. The observations of Benedict [17] and others [18] of the absence of azotemia in patients who exhibited neuroretinitis similarly militate against the assumption that azotemia is in any way responsible for the appearance of this picture. Of interest in this connection is the fact that uremia due to various causes may be present for long periods without the coexistence of retinal lesions.[14] These views are firmly borne out by the absence of neuroretinitis in our cases of slowly progressive arteriosclerosis despite the existence of long-standing azotemia.

An additional point worthy of comment is the possible differential diagnostic value of neuroretinopathy in instances of hypertension. Keith, Wagener and Kernohan [11] originally averred that a clinical differentiation between chronic diffuse glomerulonephritis and malignant

14. Fishberg, A. M., and Oppenheimer, B. S.: The Differentiation and Significance of Certain Ophthalmoscopic Pictures in Hypertensive Diseases, Arch. Int. Med. **46**:901 (Dec.) 1930.

15. Fishberg, A. M.: Hypertension and Nephritis, ed. 4, Philadelphia, Lea & Febiger, 1939.

16. Behan, J. L.: The Fundus Changes in Nephritis, J. A. M. A. **78**:1691 (June 3) 1922.

17. Benedict, W. L.: Retinitis Associated with Disease of the Cardiovascular System, New York M. J. **117**:741, 1923.

18. (*a*) Volhard, F.: Ueber die Retinitis Albuminurica, Verhandl. d. deutsch. Gesellsch. f. inn. Med. **33**:422, 1921. (*b*) Wagener, H. P., and Keith, N. M.: Cases of Marked Hypertension, Adequate Renal Function and Neuroretinitis, Arch. Int. Med. **34**:374 (Sept.) 1924. (*c*) Fishberg.[15]

hypertensive vascular disease might be made ophthalmoscopically on the basis of the color of the disk, the presence of arteriosclerosis, the extent of retinal edema and types of exudate. However, the criteria proposed by these authors were not applicable in many of our cases. Furthermore, the malignant neuroretinopathic picture has been found to exist not in these entities alone but in other diseases in which severe hypertension supervenes. Longcope,[19] for example, has observed a striking relation between arteriolar lesions of the fundus—"hemorrhagic retinitis"—and hypertension in instances of pyelonephritis. Moreover, the occurrence of neuroretinitis in cases of neoplasm of an adrenal, polyarteritis nodosa, polycystic kidneys and even renal amyloidosis in which severe hypertension supervenes is well known. Accordingly, the supposed differential diagnostic importance of the retinal findings would appear to be nullified. Cannady and O'Hare,[12] Baehr [6] and Fishberg [15] have similarly negated the possibility of differentiation in most cases of hypertension on the basis of the ophthalmoscopic picture alone.

It is worthy of reemphasis that the neuroretinopathy of hypertensive patients is in no way induced by the azotemia but is rather the expression of an increased intracranial pressure [20] or is incident to the occurrence of ocular vascular lesions and should be viewed as evidence of the accelerated or malignant phase of hypertension no matter what its basic cause might be. It appears more accurate, then, to refer to the full development of this clinical picture in which severe hypertension and papilledema exist as the syndrome of "malignant hypertension" [18b] possibly associated with accelerated arteriosclerosis, and the presence of all disease entities which are capable of producing this clinical picture should be duly suspected.

PATHOLOGIC VASCULAR CHANGES

The vascular pictures of the three groups presented striking histologic differences.

Slowly Progressive, or "Negative," Type.—The vascular lesions in the first group consisted of slight to occasionally severe intimal thickening of the interlobular arteries with associated narrowing of their lumens. The thickening was callus in type, with only here and there a fibroblast or two. The focal cellular change was noted only within the intima of the larger arteries and because of its sparsity was believed to convey no significance. Kimmelstiel and Wilson [4] considered limited cellular pro-

19. Longcope, W. T.: Chronic Bilateral Pyelonephritis: Its Origin and Its Association with Hypertension, Ann. Int. Med. **11**:149, 1937.

20. Kessler, M. M.; Moschcowitz, E., and Savitsky, L.: The Hematoencephalic Barrier: The Study of the Clinical Aspects and the Mechanism of the Development of Hypertension of the Cerebrospinal Fluid in Hypertensive Disease, J. Nerv. & Ment. Dis. **90**:594, 1939. Fishberg.[15]

liferations of this variety to be related to a severe degree of renal contraction. Fat deposition was noted often within the intimal layer, but hypertrophy of the medial layer was only occasionally encountered. In sections showing fibrous intimal thickening of any considerable degree medial atrophy was invariably associated.

In the main, the larger arteries showed slight to moderate hyperplasia of the internal elastic membrane and frequent fibrillar disruption, while the arterioles, including the vasa afferentia, revealed hyalinized walls and fatty change with concomitant encroachment on the lumen. In a few cases the vascular tree disclosed minimal lesions (table 1).

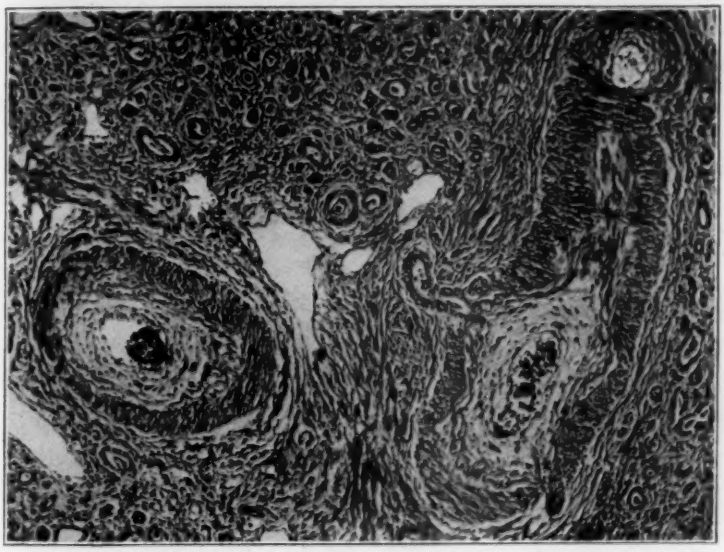

Fig. 1.—Photomicrograph (× 77) of an interlobular artery showing cellular proliferation and the looseness of the intimal layer.

Accelerated Type.—Transitional Form: This group comprises those instances in which cellular proliferation within the intimal layers of the interlobular arteries was disclosed, in addition to the alterations just outlined (fig. 1). The intimal cells were of the type noted by Klemperer and Otani,[2] i. e., "fibroblasts, which often show a reticulated arrangement, and mononuclear cells with a large amount of fat (foam cells)." Occasionally, an abundant cellular and delicate fibrillar proliferation was found in the intima of the larger arteries, with associated narrowing of the lumen (figs. 2 and 3). Scattered mural foci of calcification were present occasionally, in the smaller branches. No case in which arteriolonecrosis was present was included in this group.

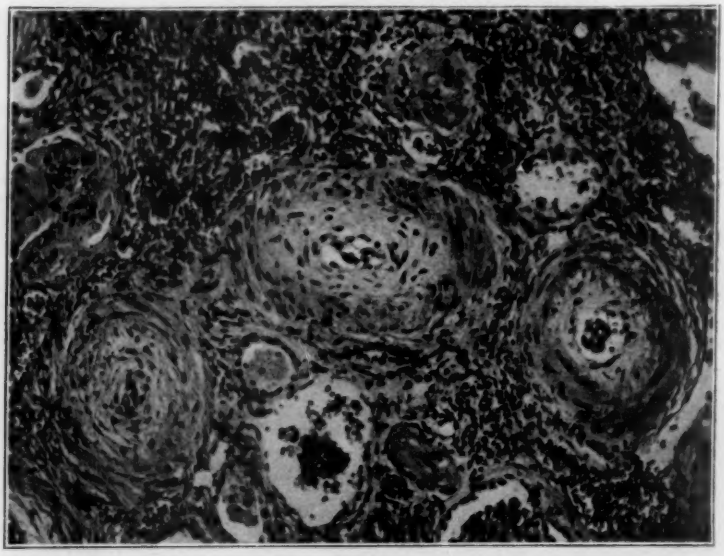

Fig. 2.—Photomicrograph (× 136) of medium-sized arteries with cellularity of the intima.

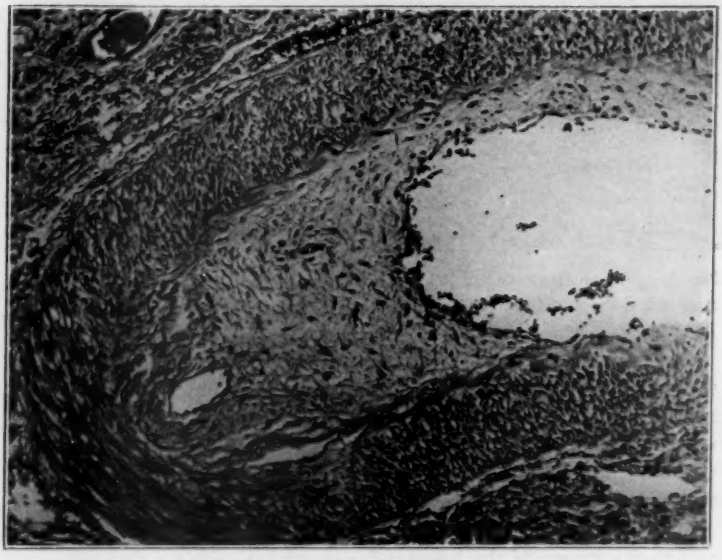

Fig. 3.—Photomicrograph (× 106) of a larger artery than those in figures 1 and 2, showing cellularity of the intima associated with conspicuous delicate fibrillar transformation.

The term transitional is purely arbitrary and has been chosen to designate those instances which we believe represent the anatomic transformation from the slowly progressive to the most advanced malignant (accelerated) phase of the disease. These cases were also designated thus to stress the interesting and important fact that a clinical picture of malignant disease may be observed in subjects who merely present conspicuous cellular intimal proliferations and no arteriolonecrotic lesions. Moreover, such a grouping serves to indicate that the intimal cellularity, edema and associated encroachment on the lumen are the precursors of the necrotic arteriolar alterations.

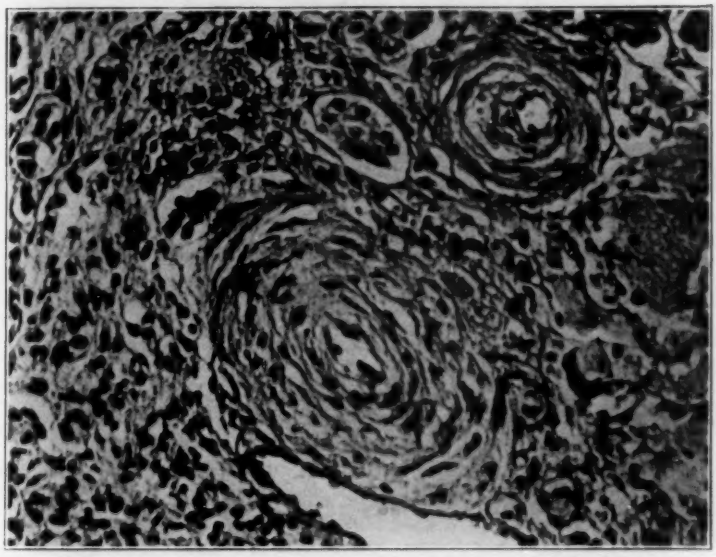

Fig. 4.—Photomicrograph (× 335) of interlobular arteries exhibiting an "onion peel" type of cellular proliferation of the intima with severe encroachment of the lumen. Note the looseness of the intima in the smaller artery.

Advanced Form: Arterial sections disclosed changes which were described both for the negative and for the transitional group. In the cases in the advanced group, however, even more prominent cellular proliferation was exhibited than was encountered in cases of the transitional phase, with more severe encroachment on the lumen. Frequently the cellular proliferations of the medium-sized and larger arteries were "nodular" in type, often concentric with uniform thickening of the wall of the vessel (fig. 4). Occasionally, due to the intimal edema and cellularity, the lumen was virtually occluded, while here and there com-

plete obliteration of the lumen had taken place. The cellularity of the intima was not confined to the interlobular arteries but was observed to have involved the walls of the arterioles and often of the arcuate

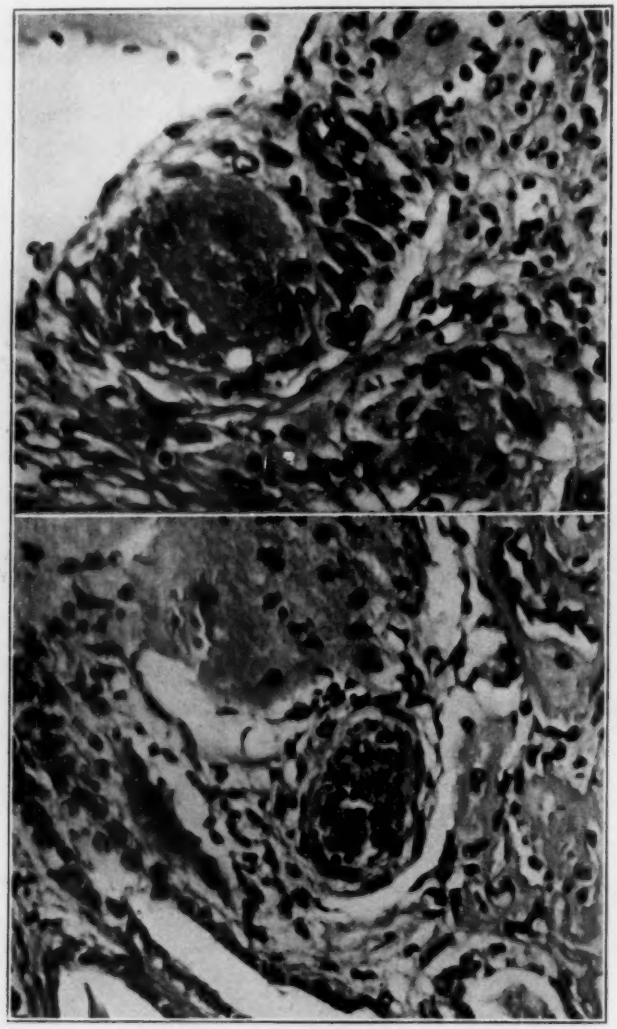

Fig. 5.—Photomicrograph (× 400) of arterioles presenting extensive necrosis and impregnation of the wall with erythrocytes.

vessels. A necrotizing arteritis similar to the type seen in the more acute form of the disease was observed in 1 case.

We were not impressed with any perivascular cellular collections which might be ascribed to the intimal alterations. If a perivascular infiltration was present, it was usually in those cases in which the inflammatory changes throughout the kidney were prominent. Consequently, such interstitial cellular reactions were ascribed to the basic generalized inflammatory renal involvement rather than to the presence of vascular abnormalities.

The arterioles and frequently the distal portions of the interlobular arteries were the seat of "fibrinoid" intimal transformations, diffusion of blood elements, mural necrosis, cellular degeneration and partial to

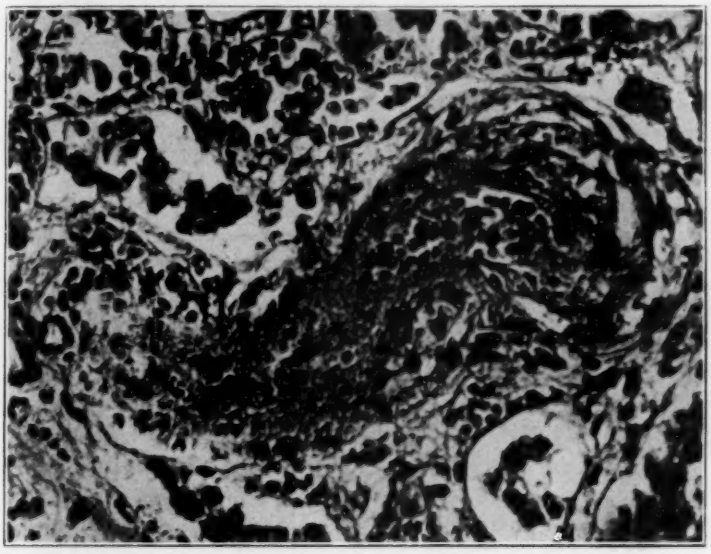

Fig. 6.—Photomicrograph (× 480) of a small interlobular artery showing widespread necrosis of the wall and associated diffusion of erythrocytes.

complete occlusive thromboses of their lumens (figs. 5 and 6). Arteriolar necrosis and rarely focal intimal necrosis of the smaller interlobular arteries were encountered in all cases which comprise this group. A periarteriolar polymorphonuclear reaction was seen only rarely. Occasionally, where the preglomerular portion of the vas afferens had become necrotic, extension of this process into the intraglomerular portion was observed. Here and there focal endothelial proliferation of various-sized arteries was also present. Rarely, fibrotic thickening of the walls of large veins was encountered, and in 2 instances, organizing venous thrombosis. In 1 case a so-called periarterial "granuloma" was

found consisting of newly formed capillaries, edematous connective tissue and infiltrating lymphocytes and polymorphonuclear leukocytes.

The lesions of the remaining structural units of the kidneys are too well known to be discussed here. It is worthy of mention, however, that in the accelerated group scattered areas of glomerular tuft necrosis were seen which were indistinguishable from those glomerular alterations that occur in the malignant phase of essential hypertension. Frequent intraluminal tubular collections of polymorphonuclear leukocytes were observed. In an occasional case low grade pyelonephritis was in evidence microscopically but was not considered to have contributed significantly to the renal alterations. The presence of polymorphonuclear leukocytes within the tubular lumen may be attributed not only to glomerular inflammation and coexistent pyelonephritis but to the internal hydronephrosis secondary to renal fibrosis. The analysis of our cases on the basis of the pathologic findings suggested the classification employed in table 4.

TABLE 4.—*Incidence of the Various Types of Arterial Change in Forty-Nine Cases of Chronic Diffuse Glomerulonephritis*

Type of Arterial Change	Number of Cases	Percentage of Cases
Slowly progressive arteriosclerosis	14	28.5
Accelerated arteriosclerosis		
Transitional phase	13	26.5
Advanced phase	22	45.0

DISTRIBUTION OF THE ARTERIAL LESIONS

Although the arterial lesions occurred more often and were most conspicuous within the kidney, they were not confined to that organ but presented a generalized distribution similar to that described by Fishberg.[21] The extrarenal vascular alterations in all groups consisted mainly of slight to moderate intimal thickening, elastosis and scattered foci of hyalinization.

Arterial lesions characteristic of accelerated arteriosclerosis in organs other than the kidneys were encountered less frequently. Scattered medium-sized arteries of the pancreas not uncommonly showed asymmetric intimal proliferations, foam cells and edema. Arteriolonecrosis was found in only 6 cases in extrarenal locations. In 2 instances arteriolar necrosis and a reactive polymorphonuclear infiltrate were encountered within the pancreas, while in 2 cases focal pancreatitis and

21. Fishberg, A. M.: Anatomic Findings in Essential Hypertension, Arch. Int. Med. **35**:650 (May) 1925; footnote 3.

interstitial hemorrhages were observed, presumably the result of the vascular alterations. In 1 case thrombosis of the lumen of a medium-sized artery had occurred due to intimal and endothelial abnormalities. In 2 other subjects accelerated arterial lesions were present in the testes, stomach and adrenals.

CLINICOPATHOLOGIC SIGNIFICANCE OF ARTERIOPATHIES

Jores [22] was the first to stress the occurrence of generalized arteriosclerosis in subjects with glomerulonephritis and maintained that these vascular alterations might play a role in the clinical course of the disease. Baehr and Ritter [23] later demonstrated by means of perfusion experiments that a reduction in renal vasculature was characteristic of contracted kidneys and reported extensive renal arterial lesions in cases of chronic glomerulonephritis. That the vascular changes constituted an important factor in renal contraction in cases of glomerulonephritis was reiterated. The opinion was also posed that "this may help to explain why the clinical pictures in the advanced stages of both primary contracted and secondarily contracted kidney cannot be differentiated." Elwyn [24] and Weiss and Parker [25] similarly suggested that the arterial lesions which occurred in glomerulonephritis exaggerated the glomerular ischemia. These opinions were concurred in by Wagener and Keith,[5] who stated that when the sclerotic lesions occur in glomerulonephritis "they indicate that the nephritis had been complicated by the development of diffuse arteriolar lesions which from then on assume the dominant role in the progress of the disease." Fishberg [15] voiced a similar opinion.

The frequency with which severe vascular lesions may occur in instances of chronic diffuse glomerulonephritis is indicated by the observations which constitute the basis of this paper. In a group of 49 cases, advanced arterial changes were exhibited in 35, or 72 per cent (table 4). Correspondingly, the clinical course of illness in those cases in which the accelerated vascular lesions were encountered at necropsy was strikingly more severe than that in the cases in which this arteriopathy was absent. The constancy of the association of accelerated vascular lesions with a rapidly developing clinical course indicates that the anatomic lesions constitute an important mechanism in the intensification and progression of the clinical picture.

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22. Jores, L.: Ueber die Arteriosklerose der kleinen Organarterien und ihre Beziehungen zur Nephritis, Virchows Arch. f. path. Anat. **178**:367, 1904.

23. Baehr, G., and Ritter, S.: The Arterial Supply of the Kidney in Nephritis, Arch. Path. **7**:458 (March) 1929.

24. Elwyn, H.: Diffuse Glomerulonephritis, Am. J. M. Sc. **165**:366, 1923.

25. Weiss, S., and Parker, F., Jr.: Pyelonephritis: Its Relation to Vascular Lesions and to Arterial Hypertension, Medicine **18**:221, 1939.

ETIOLOGY OF VASCULAR LESIONS

The vascular picture which we have encountered in our cases of chronic diffuse glomerulonephritis has been noted by a number of investigators and has been variously referred to either as productive endarteritis or as "endarteritis obliterans." These alterations have been attributed by some either to the presence of inflammatory changes or to the result of glomerular obstruction to blood flow [15] or to both.[23]

That obstruction to arterial blood flow of itself is an essential factor in the production of the accelerated type of lesion is negated by the fact that this picture is not observed in a disease, such as renal amyloidosis, in which glomerular obstruction is characteristically present,[26] unless, as we have seen, hypertension supervenes.

Weiss and Parker,[25] on the other hand, have implied an inflammatory origin for this variety of arteriopathy. In their cases, significantly, when hypertension was present, the vascular changes were found to be even more advanced and diffuse. That renal vascular changes may be of inflammatory origin and may even occur in the acute and the subacute phase of diffuse glomerulonephritis has been well recognized since Löhlein's [27] vivid description. The alterations which he described, however, were in the nature of arteriolitis or occasionally arteritis, with extensive necrosis of the wall, reactive polymorphonuclear leukocyte infiltrations and thrombosis of the lumen of the affected vessel. Vascular changes of this type were encountered in some of the cases of acute and of subacute glomerulonephritis which we reviewed as control material. It was apparent to us, however, that the type of lesion which Löhlein described in no way resembled the changes to which we specifically refer in this presentation. Moreover, the remarkable similarity of the arterial pictures of this phase of renal disease to those of unequivocal noninflammatory renal diseases, such as the kidney of essential hypertension, vitiates the contention that inflammation plays an important role in their morphogenesis. It may be argued further in this connection that if the inflammatory changes of the renal parenchyma were significantly concerned in the formation of the cellular arterial proliferations and the arteriolar necrosis, one would expect this type of lesion to occur not only in the earlier stages of glomerulonephritis but more widely and more frequently. Indeed, instances of chronic diffuse glomerulonephritis

26. Janeway, T. C.: Nephritic Hypertension: Clinical and Experimental Studies, Am. J. M. Sc. **145**:625, 1913.

27. Löhlein, M.: Ueber die entzündlichen Veränderungen der Glomeruli der menschlichen Nieren und ihre Bedeutung für die Nephritis, Arb. a. d. path. Inst. zu Leipzig **4**:1, 1907.

in which the vascular alterations have been either minimal or wholly insignificant in character have been repeatedly observed by others [28] and by ourselves.

It may be stated, then, that the inflammatory process does not sufficiently account for the vascular lesions of accelerated arteriosclerosis described here, and the explanation, consequently, must be sought elsewhere. The possibility has also been suggested that hypothetic toxic material which originates in the presence of renal insufficiency is an etiologic force in the production of these lesions. That the vascular alterations, however, are not the result of such a mechanism is suggested by their absence in the slowly progressive group, since in all cases in this group the subjects had manifested varying degrees of azotemia. Furthermore, we have observed instances of malignant hypertension with renal arterial lesions of the identical form described in our cases of nephritic disease in which death was the result either of cerebral or of cardiac episodes and in which there was no evidence of renal insufficiency. The occurrence of arteriolonecrosis in the absence of renal insufficiency has been previously recorded.[29] We are not in accord, therefore, with the contention of some investigators [30] that the necrotic arteriolar lesions are the effect of functional renal impairment.

In our attempt to learn what common denominator exists in the cases with accelerated arteriopathy, to which might be possibly ascribed an etiologic role, we were struck with the constant association of severe protracted hypertension. This impression found substantiation when the clinical histories and the anatomic data were reviewed in cases of malignant nephrosclerosis. Except for the fact that the vascular lesions encountered in our cases of chronic diffuse glomerulonephritis were less widespread and intense, they did not differ basically from those seen in cases of malignant nephrosclerosis. Similarly, a history of sudden augmentation of a previously high blood pressure could be elicited not infrequently, just as in our cases of nephritic disease.

In the cases with mild to moderate increased blood pressure, retinal hemorrhages and exudates and arterial narrowing, but no swelling of the optic disk, the course is relatively benign, slow and progressive. Eventually, uremia makes its appearance, occasionally in conjunction with some component of cardiac insufficiency. The dominant arterial lesion here is the same as that which is seen in instances of so-called benign essential hypertension. In direct contrast to this picture are those cases in which the blood pressure is extremely high (systolic

28. Fahr, T., in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1925, vol. 6. Jores.[22]

29. Murphy, F. O., and Grill, J.: So-Called Malignant Hypertension: A Clinical and Morphologic Study, Arch. Int. Med. **46**:75 (July) 1930. Klemperer and Otani.[2]

30. Kimmelstiel and Wilson.[4] Weiss and Parker.[25]

over 200 mm. of mercury and diastolic exceeding 120 mm.). In addition to the retinal hemorrhages, exudates and arterial narrowing, there is swelling of the optic nerve head. The latter may vary from mere blurring of the disk margins to prominent elevation of the nerve head. The circumpapillary retinal tissue is sometimes edematous, and in cases of advanced disease detachment of the retina has been encountered. The clinical course of the latter group becomes intensified with the onset of severe hypertension and characteristically terminates due to an association both of renal and of cardiac failure—a picture which is identical with that observed in malignant nephrosclerosis. The visceral lesions also are strikingly similar to those encountered in the latter disease.

The third group—the transitional—occupies an intermediate place between the slowly progressive and the advanced accelerated one. It comprises instances of chronic diffuse glomerulonephritis in which the blood pressure is usually higher than that in the slowly progressive group and may reach the heights of the advanced accelerated group. In it, however, the blood pressure is usually more labile and neuroretinopathy may not be present. The histologic picture similarly lies midway between those just described. We are of the belief that the height and lability of the blood pressure and the presence or absence of neuroretinopathy are the cardinal clinical criteria on which to base the suspicion of the presence of either the slowly progressive or the accelerated phase of the disease. No other clinical manifestation (degree of azotemia, anemia or edema) can be employed in this connection.

Worthy of special mention are those cases of transitional disease in which excessive blood pressure had been present but in which anatomic lesions were encountered which were only slightly more advanced than those which were characteristic of the slowly progressive phase. It appears to us that these cases of transitional disease had reached their termination before there had been sufficient time for the development of the classic accelerated arteriopathy, which seems to indicate that severe hypertension may precede the development of the cellular and the necrotic arteriolar changes. When severe and fixed hypertension supervenes, the ischemia incident to the elevated intravascular tension is a factor in the acceleration of the tempo of the degenerative changes of the renal parenchyma, with resultant profound and irreversible disturbances of renal function.

SUMMARY AND CONCLUSIONS

A series of 49 consecutive cases of chronic diffuse glomerulonephritis was investigated, with especial attention focused on the character of the arterial changes in all viscera. An independent and thorough evaluation of the clinical data in these same cases was also made.

In accordance with the varied vascular pictures a division of the disease into a slowly progressive and an accelerated phase is proposed, 14 cases representing the former and 35 cases the latter.

The histologic vascular lesions peculiar to each group of cases are described in detail. The intimal fibrosis, elastosis of arteries and arteriolar hyalinization which were characteristic vascular alterations in the slowly progressive group were also observed in the other groups. A transitional group, in addition, exhibited cellular proliferation, foam cells and edema of the arterial intima, while the advanced accelerated group revealed an even more conspicuous cellular intimal proliferation of the arterial tree and, in addition, distinct necrosis of the arteriolar walls.

A correlation of the clinicopathologic features was then determined. In the majority of cases it was found that the intensity of the clinical picture usually paralleled the anatomic vascular changes.

Neuroretinitis, common in the transitional and the advanced accelerated group, was never observed in cases of the slowly progressive phase of the disease.

On the basis of this survey it is concluded that arterial alterations both in the transitional and in the advanced accelerated groups of cases of chronic diffuse glomerulonephritis represent the anatomic equivalents of the clinical picture which has been designated malignant hypertension. This has been shown to occur more frequently than hitherto suspected in chronic diffuse glomerulonephritis.

In view of the constancy of severe hypertension in a miscellaneous group of diseases in which accelerated arterial changes are present, this factor is considered a potent etiologic force in their production. Whether hypertension is the basic determinant for the appearance of the vascular lesion or is itself mediated through the liberation of a toxic vasopressor substance is beyond the scope of this presentation.

The tempo of the clinical course in instances of chronic diffuse glomerulonephritis may be influenced not only by the exacerbation of the inflammatory process but by the height of the blood pressure.

The occurrence of severe hypertension and neuroretinopathy in disease entities of varied pathogenetic background vitiates the belief that these criteria may be of differential diagnostic import.

The vascular lesions once established contribute importantly to the advancement of the renal process and the intensification of the clinical picture.

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PYELONEPHRITIS AND HYPERTENSION

A STUDY OF THEIR RELATION IN 11,898 NECROPSIES

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CHICAGO

The work of Goldblatt [1] has shown that hypertension can be experimentally produced in animals by decreasing or altering the blood supply to the kidneys. Soon after the announcement of his experiments there began to appear in the literature clinical counterparts of his work. Mullholland [2] reviewed the literature in this regard and classified the reported cases of hypertension resulting from interference with the blood flow through the kidneys in the following manner:

I. Intrinsic, infection within the kidney
  A. Bilateral, resulting from
    1. Benign obstruction of the prostate
    2. Partial obstruction of the ureters
    3. Accompanying condition in the bladder causing clinical pyelonephritis
      (*a*) Stone
      (*b*) Diverticulum
      (*c*) Malignant growth
    4. Bilateral infection
  B. Unilateral, resulting from
    1. Pyelonephritis
    2. Calculi
    3. Contracted kidney caused by
      (*a*) Trauma
      (*b*) Infection
    4. Tuberculosis of kidney

II. Extrinsic, effecting interference with the circulation in the renal artery
  Unilateral
    1. Malposition
    2. Abnormal course and position of artery
    3. Atheromatous plaques
    4. Infarct of the kidney
    5. Thrombosis with recanalization
    6. Hydronephrosis with pressure on artery

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1. Goldblatt, H.: Experimental Hypertension Induced by Renal Ischemia: Harvey Lecture, Bull. New York Acad. Med. **14**:523, 1938.

2. Mullholland, S. W.: Hypertension: The Problem, the Study, the Future, Bull. New York Acad. Med. **16**:244, 1940.

Among the most numerous of these are the cases of unilateral pyelonephritis associated with hypertension apparently cured by nephrectomy (McIntyre,[3] Barker and Walters,[4] Barney and Suby,[5] Boyd and Lewis,[6] Butler[7] and Leadbetter and Burkland[8]).

Accepting pyelonephritis as one of the causes of disturbed renal vascular flow and thus a process capable of invoking hypertension, Weiss and Parker[9] have attempted to explain and correlate the frequent finding of vascular changes of the kidney in 100 cases of pyelonephritis and hypertension. Their results were constant and seemed to show a distinct relation to the degree of hypertension and the age of the infection. Though their study deals with the entire field of pyelonephritis, the most noteworthy part is that regarding hypertension. They observed elevation of blood pressure especially in the healed and the chronic stage of the infection and were able to describe the vascular lesions in great detail. Their dissociation of the intimal thickening and hyalinization as a result of involutionary changes from productive endarteritis, hyperplastic arteriolosclerosis and necrotizing arteriolitis which they were able to identify only in cases of pyelonephritis, and these were most pronounced in the infected and scarred portions of the kidneys, seems to prove that the vascular lesions are the result of the infection and probably a factor in the production of hypertension. They found similar lesions, though of a lesser degree, in cases of infection without hypertension and concluded that the lesions occur before the hypertension develops. The subsequent hypertension apparently aggravates the lesions, which in turn aggravate the high blood pressure, thereby provoking a vicious cycle.

The purpose of this study is to examine critically the autopsy records of a large series of patients and to correlate the incidence of hypertension and pyelonephritis. Records of patients with hydro-

3. McIntyre, D. W.: Unilateral Pyelonephritis with Hypertension: Apparent Cure After Nephrectomy, J. Urol. **41**:900, 1939.

4. Barker, N. W., and Walters, W.: Hypertension Associated with Unilateral Chronic Atrophic Pyelonephritis: Treated by Nephrectomy, Proc. Staff Meet., Mayo Clin. **13**:118, 1938.

5. Barney, J. D., and Suby, I. H.: Unilateral Renal Disease with Hypertension: Report of a Case Apparently Cured by Nephrectomy, New England J. Med. **220**:744, 1939.

6. Boyd, C. H., and Lewis, L. G.: Nephrectomy for Arterial Hypertension, J. Urol. **39**:627, 1938.

7. Butler, M.: Chronic Pyelonephritis and Arterial Hypertension, J. Clin. Investigation **16**:889, 1938.

8. Leadbetter, W. F., and Burkland, C. E.: Hypertension in Unilateral Renal Disease, J. Urol. **39**:611, 1938.

9. Weiss, S., and Parker, F., Jr.: Pyelonephritis: Relation to Vascular Lesions and to Arterial Hypertension, Medicine **18**:221, 1939.

nephrosis, nephrolithiasis and horseshoe kidney were also studied to complete the picture. The relation of renal vascular lesions to hypertension, especially as regards age and the state of vascular tension, as well as sex and race, were particularly noted. It is thought that such a study of a large series of patients may contribute to the collection of statistical information already begun by such observers as Weiss and Parker and the Mount Sinai group in New York,[10] as well as by the group at the Mayo Clinic [11] and others.

All instances of pyelonephritis were studied from records of 11,898 consecutive patients who came to autopsy at the Cook County Hospital in the ten year period 1930 to 1939 inclusive. These patients were tabulated according to age, sex, race and the state of vascular tension. The patients with unilateral and with bilateral involvement of the kidneys were separated. The complete autopsy protocol, which at the Cook County Hospital consists of an abstract of the clinical history and course of the disease, a description of the body as a whole, a gross description of each organ, an objective description of the microscopic appearance of the pertinent organs and a detailed anatomic diagnosis, was examined critically. For criteria of hypertension a persistent systolic pressure of 150 mm. of mercury and a diastolic pressure of 95 mm. were selected; these are well above the limits accepted by the American Heart Association.[12] A hypertrophied left ventricle and increased weight of the heart in the absence of other known causes was considered substantiating evidence. If the recorded blood pressure was a terminal one or was equivocal, the anatomic evidence was accepted.

There were 290 patients with pyelonephritis, constituting 2.5 per cent of the total number. Of these, the condition was bilateral in 224 and unilateral in 66. The patients with bilateral disease constituted 77 per cent of those with pyelonephritis and 1.7 per cent of all the patients in the series. There were 130 females and 160 males, 44.8 and 55.2 per cent, respectively. This is more or less in accord with the proportion of adult males and females on whom autopsy was done.

10. Oppenheimer, B. S.; Klemperer, P., and Moschowitz, L.: Evidence for Goldblatt Mechanism for Hypertension in Human Pathology, Tr. A. Am. Physicians **54**:69, 1939.

11. Braasch, W. F.; Walters, W., and Hammer, H. J.: Hypertension and the Surgical Kidney, Proc. Staff Meet., Mayo Clin. **15**:477, 1940. Barker, N. W., and Walters, W.: Hypertension and Chronic Atrophic Pyelonephritis, ibid. **15**: 475, 1940. Braasch, W. F., and Jacobson, C. E.: Chronic Bilateral Pyelonephritis and Hypertension, ibid. **15**:481, 1940.

12. New York Heart Association, Criteria Committee. Nomenclature and Criteria for Diagnosis of Diseases of the Heart, ed. 4, New York, New York Tuberculosis and Health Association, 1939.

Of the 290 patients, 200, or 68.9 per cent, were white and 90, or 31.1 per cent, were Negro.

The patients were arbitrarily divided into six age groups: 30 and under, 31 to 40, 41 to 50, 51 to 60 and over 60. Thirty-six patients were under 30, of which 13 were male and 23 female. Between the ages of 31 to 40 there were 45 patients, of which 14 were male and 31 female. In the group from 41 to 50 there were 56, more or less equally divided between the sexes. In the 51 to 60 group there were 65, of which 35 were male and 30 female. In the patients over 60 there were 69 men and 19 women. The preponderance of males in the total number of patients with pyelonephritis is made up mainly by those in the older age groups. The incidence of pyelonephritis in the young women not only fits in with expectations but explains to a great extent the mortality. One can almost assume from these figures that fewer women survive such renal infection and live to be autopsied in the

TABLE 1.—*Incidence of Hypertension in the Various Age Groups in Two Hundred and Ninety Patients with Pyelonephritis*

Age Group	Hypertension, %	Renal Vascular Damage, %
Under 30	28.0	29.0
31-40	33.3	33.3
41-50	41.0	49.0
51-60	49.0	56.0
Over 60	63.0	69.0
Average	44.4	50.6

aged group. Though it was impossible to separate in this study the patients with acute, chronic and healed pyelonephritis, it is likely that the young women died in the acute stage. The incidence of pregnancy in these women was not ascertained, but the great preponderance of the disease in the women of child-bearing age is of some significance.

Forty-four and four-tenths per cent of all of the patients regardless of age, sex and race had an elevation of blood pressure. However, the significant findings are those seen in the incidence of hypertension in the various age groups (table 1). From 28 per cent in the youngest group the incidence rises in direct proportion to age until it reaches 63 per cent in the oldest group. Similarly, the incidence of renal vascular changes, which in this series includes all the various types described by Weiss and Parker with few patients showing only one distinct type, is completely parallel with that of hypertension. It increases from 29 per cent in those under the age of 30 to 69 per cent in those over 60. The greatest incidence of pronounced hypertension was found in the atrophic kidneys of patients with old pyelonephritis with microscopic pictures of well advanced arteriolosclerosis.

Of the 66 patients with unilateral pyelonephritis, 22, or 33.3 per cent, had an elevated blood pressure (table 2). The greatest incidence of hypertension occurred in the 41 to 50 age group, being 35.7 per cent, as compared to 28.5 per cent in the youngest group. In the category of bilateral pyelonephritis 107 patients, or 47.7 per cent, had high blood pressure. The percentage ranged from 27.5 in the youngest group to 63.7 in the oldest one. It appears that any increased incidence of

TABLE 2.—*Relation of Hypertension to Unilateral or Bilateral Involvement of the Kidneys in Two Hundred and Ninety Patients with Pyelonephritis*

	Unilateral Involvement			Bilateral Involvement		
	Elevated Blood Pressure		Normal Blood Pressure:	Elevated Blood Pressure		Normal Blood Pressure:
Age Group	No. of Patients	Percentage	No. of Patients	No. of Patients	Percentage	No. of Patients
Under 30	2	28.5	5	8	27.5	21
31-40	3	33.3	6	12	33.3	24
41-50	5	35.7	9	18	42.8	24
51-60	6	35.3	11	26	54.2	22
Over 60	6	31.5	13	43	63.7	26
Total.....	22	33.3	44	107	47.7	117

TABLE 3.—*Relation of Hypertension to Sex in Two Hundred and Ninety Patients with Pyelonephritis*

	Male			Female		
	Elevated Blood Pressure		Normal Blood Pressure:	Elevated Blood Pressure		Normal Blood Pressure:
Age Group	No. of Patients	Percentage	No. of Patients	No. of Patients	Percentage	No. of Patients
Under 30	5	38.4	8	5	21.7	18
31-40	5	35.7	8	10	32.2	21
41-50	14	48.2	15	9	33.3	18
51-60	21	60.0	24	11	36.6	19
Over 60	42	62.1	27	7	36.8	12
Total.....	87	54.3	83	42	32.9	88

hypertension in patients with pyelonephritis occurs mainly in those in whom the kidneys are bilaterally involved, as compared to those in whom involvement is unilateral.

The relative preponderance of pyelonephritis in young women as compared to its incidence in young men has already been mentioned. Only 32.9 per cent of the women had hypertension, as compared to 54.3 per cent of the men. This relative infrequency of high blood pressure in females as compared to that in males persists through all the age groups except that of 31 to 40, in which the difference is not striking (table 3). Among the Negroes there appeared to be a greater

incidence of hypertension in patients 31 to 50 years of age as compared to that in white persons of the same age, though the total incidence is 46.5 per cent in the white patients and 40 per cent in the Negroes (table 4).

Seventeen patients in the series had horseshoe kidney, 13 males and 4 females. Of these, 11, or 64.7 per cent, had elevated blood pressure (table 5). In these, discounting the single patient under the

TABLE 4.—*Relation of Hypertension to Race in Two Hundred and Ninety Patients with Pyelonephritis*

	Negro			White		
	Elevated Blood Pressure		Normal Blood Pressure:	Elevated Blood Pressure		Normal Blood Pressure:
Age Group	No. of Patients	Percentage	No. of Patients	No. of Patients	Percentage	No. of Patients
Under 30	3	21.4	11	7	31.8	15
31-40	9	39.0	14	6	27.2	16
41-50	9	45.0	11	14	38.8	22
51-60	8	44.4	10	24	51.0	23
Over 60	7	46.6	8	42	57.5	31
Total.....	36	40.0	54	93	46.5	107

TABLE 5.—*Incidence of Hypertension in Seventeen Patients with Horseshoe Kidney, Thirteen Patients with Polycystic Kidney and Sixty-Two Patients with Nephrolithiasis*

	Horseshoe Kidney		Polycystic Kidney		Nephrolithiasis	
Age Group	Elevated Blood Pressure	Normal Blood Pressure	Elevated Blood Pressure	Normal Blood Pressure	Elevated Blood Pressure	Normal Blood Pressure
Under 30.....	1	0	1	0	2	2
31-40.....	1	1	2	0	4	7
41-50.....	4	1	1	4	6	6
51-60.....	2	2	2	2	8	10
Over 60.....	3	2	0	1	13	4
Total.....	11 (64.7%)	6	6 (46.15%)	7	33 (53.2%)	29

age of 30, the greatest incidence of high blood pressure occurred in patients between the ages of 41 to 50, of whom 4 of 5 had hypertension. Here again the finding of vascular sclerosis was directly proportional to the incidence of hypertension. Thirteen, or 0.11 per cent, of the 11,898 patients in the series had polycystic kidneys; 10 patients were male, and 3, female. Of these, 7, or 53.7 per cent, had an elevated blood pressure. The renal vascular damage in these patients was not outstanding, 6 of 13 showing no particular parenchymal changes except atrophy in cases of severe disease. It may be pointed out that the hypertension resulting from polycystic kidney is thought to occur

differently from that of pyelonephritis. It is said to be the result of pressure of the cysts extrinsically on the renal artery. The lack of renal vascular damage in these patients corresponds with Goldblatt's finding of the relative absence of such damage in the ischemic kidneys of his dogs. Sixty-two patients had nephrolithiasis, comprising 0.52 per cent of the total number of patients. It was unassociated with evident pyelonephritis, the patients in this study with both conditions being included among those with pyelonephritis. Of these, 43, or 53.2 per cent, had an elevated blood pressure.

Braasch in his control series of 975 patients admitted to the Mayo Clinic found 20 per cent had hypertension, as compared to 26 per cent of 180 patients with pyelonephritis. The incidence of hypertension both in the control series and in the patients with renal disease increased with the age of the patients. In the youngest group there was an incidence of 8.4 per cent in the controls, as compared to 13.3 per cent in those persons with pyelonephritis; while in the oldest patients the incidences were 47.1 and 53 per cent, respectively. Oppenheimer, Klemperer and Moschowitz [10] selected every fifteenth patient in their series of 5,000 who came to autopsy and found 24 per cent had high blood pressure, as compared to 40 per cent of 97 patients with pyelonephritis. For control of the study reported here approximately 1,000 of some 12,000 patients on whom autopsy was performed during the ten year period were selected at random and classified according to age group and sex, as well as the presence or absence of hypertension. The same standards were used in the tabulation of the control patients as were used for patients with pathologic conditions. Though no exact tally was kept, approximately every tenth to fifteenth patient in the entire group of 11,898 was selected. It is felt that the resultant group represents a good cross section of the autopsy material at the Cook County Hospital and serves as a good basis for comparison. In the entire group 331 patients of 947, or 34.9 per cent, had an elevation of blood pressure. If one segregates these patients into the age groups used in the study, the percentage incidence of hypertension is under 30, 15.6; 31 to 40, 28.1; 41 to 50, 40; 51 to 60, 36.6, and over 60, 43.1. In the males the incidence in the same groups is 21.4, 25.5, 39.8, 33.5 and 43.7. In the females it is 10, 30.6, 40.2, 43.07 and 42.1 (table 6).

On the surface it would appear that 44.4 per cent of patients with pyelonephritis, 53.2 per cent of those with nephrolithiasis, 64.7 per cent of those with horseshoe kidney and 53.8 per cent of those with polycystic kidney showed an elevation of blood pressure, as compared to 34.9 per cent of a control group. The number of patients with polycystic kidney is too few for analysis. In the patients with pyelonephritis there appears to be a distinct increase in the incidence of hypertension

as compared to that in the controls except in the age group 31 to 50, in which the incidence is almost parallel. Comparing the female patients with pyelonephritis with the female controls the incidence seems to be greater only in the youngest group, in which it is 21.7 per cent, as compared to 10.0 per cent. Indeed, in the women over 40 the incidence of high blood pressure is greater in the control group. However, in the men the incidence of hypertension is greater in comparison in all the age groups and is most marked in men over 40. This apparently occurs in patients in whom both kidneys are involved, those with unilateral involvement showing no distinct variation. Though only 64 patients had uncomplicated nephrolithiasis, the incidence of hypertension was more striking than in those with the

TABLE 6.—*Relation of Hypertension to Sex and Age in One Thousand Control Patients*

	Male			Female		
	Elevated Blood Pressure		Normal Blood Pressure:	Elevated Blood Pressure		Normal Blood Pressure:
Age Group	No. of Patients	Percentage	No. of Patients	No. of Patients	Percentage	No. of Patients
Under 30	12	21.4	44	6	10.0	53
31-40	24	25.5	70	23	30.6	52
41-50	57	39.8	86	31	40.2	46
51-60	46	33.5	91	28	43.1	37
Over 60	69	43.7	89	35	42.1	48
Total.....	208	35.3	380	123	34.9	236

other diseases, being 53.2 per cent of all the patients, compared to 34.9 per cent of the controls.

The increasing incidence of hypertension with age in all the patients is of some significance. Two possible explanations may be offered. The frequency with which high blood pressure occurs in elderly persons without renal damage may suggest that even without pyelonephritis hypertension would have been present (this seems to be borne out by the controls), and therefore pyelonephritis is not an important factor in the production of their hypertension. The other explanation is that the occurrence of a much greater incidence of hypertension in the older age groups is in complete accord with the concept that the time element is important in the evolution of the hypertension associated with pyelonephritis. This material does not show how long the patients had had their renal infection, but one may assume that a patient over 60 has had it longer than a patient under 30. If one remembers that these studies are based on autopsy records, and that the young patients either did not survive their renal infection or succumbed to an unrelated

disease process, it is easily understood that the time element as regards the age of the infection may be of some importance in the production of hypertension. The apparent paradox of the women over 40 in the control group having a greater incidence of hypertension than the similar group with pyelonephritis can be rationalized. The control patients being a cross section of all those who came to autopsy include ones with all types of hypertension; some of them may be duplications as the result of pyelonephritis. In women over 40 degenerative diseases, some of which are accompanied by hypertension, are apt to occur. In addition, the great incidence of pyelonephritis in young women seems to indicate that fewer women survive their infection and live long enough to be autopsied in an older age group. If this is true, then the women over 40 in the control group are patients who not only survived their renal infection long enough for hypertension to develop but lived long enough to have an elevated blood pressure from other causes.

SUMMARY

The incidence of hypertension in patients with pyelonephritis was studied from 11,898 autopsies performed in a ten year period. In these the incidence was 44.4 per cent as compared to 34.9 per cent in a control group selected at random. In an analysis, however, this greater incidence apparently occurred in patients with bilateral pyelonephritis, especially in the male sex, and was most marked in men over 40. The relative absence of high blood pressure in patients with unilateral pyelonephritis was striking. The incidence of hypertension increased with the age of the patient and was parallel to the incidence of marked renal vascular damage. In small groups of patients with polycystic kidney, horseshoe kidney and uncomplicated nephrolithiasis the incidence of hypertension was 46.15, 64.7 and 53.25 per cent respectively.

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INTERMITTENT FEVER OF UNKNOWN ORIGIN

RECURRENT HIGH FEVER WITH BENIGN OUTCOME IN A PATIENT WITH MIGRAINE AND NOTES ON "NEUROGENIC" FEVER

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"Neurogenic" fever is a term the limits of which have not been clearly defined. Lesions of the brain stem or the hypothalamus are known to be associated frequently with pyrexia.[1] Typhoid vaccine and other foreign protein agents cause fever probably by functional alterations in the central nervous system.[2] Whether this effect occurs by virtue of changes in circulation or by direct chemical action on cells of the thermoregulatory apparatus is not yet clear. Even less clear is the mechanism responsible for elevations of body temperature accompanying emotional disturbances. The fact that they do occur, however, has long been known. Most of the writing on the subject has appeared in the German literature. Friedmann and Kohnstamm[3] in 1914 recognized that fever frequently accompanied excitement and emotional tension in the absence of physical overactivity. Seven years later Eichelberg[4] was able to induce temperatures up to 39.2 C. (102.5 F.) in patients by hypnosis. Since then pyrexia has been observed in a variety of emotional settings. Osler[5] recognized it as a manifestation of "hys-

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Dr. Herbert S. Ripley saw the patient frequently in consultation and supplied some of the data regarding his personality.

1. Kleyntyens, F.: Recherches sur la physiopathologie des centres thermorégulateurs, Compt. rend. Soc. de biol. **132**:55, 1939.

2. Ranson, S. W.; Clark, G., and Magoun, H. W.: Effect of Hypothalamic Lesions on Fever Induced by Injection of Typhoid-Paratyphoid Vaccine, J. Lab. & Clin. Med. **25**:160, 1939.

3. Friedmann, M., and Kohnstamm, O.: Zur Pathogenese und Psychotherapie bei Basedowscher Krankheit, Ztschr. f. d. ges. Neurol. u. Psychiat. **23**:357, 1914.

4. Eichelberg: Durch Hypnose erzeugtes "hysterisches Fieber," Deutsche Ztschr. f. Nervenh. **68**:352, 1921.

5. Osler, W.: The Principles and Practice of Medicine, ed. 3, New York, D. Appleton and Company, 1898.

teria." Reimann [6] found low grade temperature elevations in a group of psychoneurotic patients who showed tachycardia, wide pupils, dry mouth and hypoperistalsis. Dejerine [7] wrote that temperature elevations might be readily attributed to emotional causes in the absence of demonstrable physical disease. Unfortunately, reports of actual instances of such fevers are vague, and the personality reaction types in which the fevers occur are not clearly defined. On the basis of the knowledge which has accumulated already, however, it is possible to classify instances of "neurogenic" fever under four headings.

First, there is the occurrence of extremely high temperatures generally held to be incompatible with life in a person who does not otherwise appear ill. It is likely that in most cases fraud is the basis of such a fever. The second variety is habitual low grade fever.[8] The third type is manifested by isolated rises in body temperature of short duration definitely associated with some experience inducing anxiety or tension in the patient.[9] The last group includes recurrent bouts of high fever, which continue for years without apparent detriment to the patient. This communication will deal with a case of the last-named type of fever.

A competent short review of the literature on this subject between 1910 and 1933, with abstracts of illustrative cases, is available.[10] There are few reports in detail of cases of recurrent fever over a period of years which eluded explanation indefinitely on the basis of some structural disease.

Alt and Barker in 1930 [11] reported a case of intermittent fever which occurred in a 17 year old Armenian boy and which had lasted twenty-five years at the time the report was made. Attacks occurred about four times a year at first and gradually increased in frequency, until at the time the case was reported the patient was having an attack twice a week. The temperature rose to 39 C. (102.2 F.). Abdominal cramps on the right side, vomiting, pain in the knees and leukocytosis (15,000 to

6. Reimann, H. A.: Hypothermia: Subnormal Temperature and Its Relation to Neurocirculatory Asthenia, J. A. M. A. **115**:1606 (Nov. 9) 1940.

7. Dejerine, J.: Sémiologie des affections du système nerveux, Paris, Masson & Cie, 1926, p. 1070.

8. Smith, D. S.: Fever of Undetermined Etiology, J. Michigan M. Soc. **38**: 125, 1939.

9. Falcon-Lesses, M., and Proger, S. H.: Psychogenic Fever, New England J. Med. **203**:1034, 1930.

10. Dunbar, H. F.: Emotions and Bodily Changes, ed. 2, New York, Columbia University Press, 1939.

11. Alt, H. C., and Barker, M. H.: Fever of Unknown Origin, J. A. M. A. **94**:1457 (May 10) 1930.

20,000 cells) were often associated with the fever. The episode lasted about a day and was usually followed by loose stools for a day or two. Otherwise, between the attacks the patient felt perfectly well. He did not lose any weight or show any signs of infection except for an enlarged spleen. The latter was removed surgically, without effect on the bouts of fever. It weighed 544 Gm. at operation. Microscopic section revealed nothing specific or helpful diagnostically.

The next year Santos [12] reported 2 cases of a similar condition. In 1 case a 32 year old woman had recurrent febrile rises of temperature to 41 C. (105.8 F.) associated with abdominal cramps. During a period when attacks were occurring nearly every day the author found it possible to suspend them for several days with the help of hypnotic suggestion. In the second case a 24 year old woman was subject to hysterical palsies and aphonia and convulsive attacks; she also had abdominal pain in association with her fever. The fever could be controlled by injection of opiates.

Later Scott and Kirschner [13] reported a case in which attacks of fever were accompanied by an urticarial cutaneous rash, joint pains and at one time an effusion into the right knee joint.

In 1937 Allen [14] reported a case of intermittent hyperthermia of seven years' duration, which now, five years later, is the subject of the present communication.

REPORT OF A CASE

The patient, L. McC., an engineer aged 43 at the time of admission to the New York Hospital, began suffering from intermittent attacks of fever with temperatures up to 40 C. (104 F.) in 1928, and he has continued to be afflicted with them until only recently.

It is of special interest that the patient's father had suffered from similar intermittent attacks of fever with temperatures up to 40 C. associated with "sick headache," nausea and vomiting. These began at about the age of 25, lasted nearly fifteen years and finally stopped spontaneously. At first the bouts came every few weeks, but toward the end they were less frequent, occurring only two or three times a year. A sister and an aunt of the patient suffered most of their lives with periodic headaches without fever, diagnosed by physicians as migraine. At the time of the menopause the patient's mother had a mental illness which required treatment in a sanatorium for several months.

During late adolescence the patient himself began suffering from periodic headaches characterized by bifrontal pain and pain in the eyeballs, photophobia and nasal discharge. The occurrence was especially frequent at times of emotional

12. Santos, R. N.: Ueber die neuropsychogene Hyperthermie, Med. Klin. **27**: 1273, 1931.

13. Scott, J. W., and Kirschner, A.: Intermittent Fever of Three and a Half Years' Duration, Lancet **2**:299, 1938.

14. Allen, E. V.: Intermittent Hyperthermia of Seven Years' Duration, Ann. Int. Med. **10**:1204, 1937.

strain. In 1922, at 25 years of age, during a period of marked anxiety in a setting of business problems he became nearly incapacitated by these headaches. Twelve years before admission to the New York Hospital, at the age of 31, the patient suddenly ceased to have the headaches and he began to experience recurrent attacks of a different nature, characterized by fever, malaise and aches and pains in his back and extremities. One or two days after his first episode he felt well again. Six weeks later a second attack occurred. From then on he had recurrent bouts of fever with progressively shorter intervals between them, until at the time of admission to the New York Hospital he was having one a week. Before each episode for a day or less there were prodromal symptoms consisting of aches in the ankles and the spine, a feeling of mental unrest and difficulty in concentration. The fever was often ushered in by a shaking chill. The temperature rose rapidly to a peak and returned to normal within twelve hours. Leukocytosis (in the neighborhood of 15,000 cells) occurred. The episodes associated with marked elevation of temperature, to about 40 C., were of shorter duration and caused less discomfort than those in which the fever was of relatively low grade or was artificially depressed by antipyretic drugs. After the fevers he had a "purged" feeling, with a sense of especial well-being and mental efficiency. From this point on, he could do his work effectively until the prodromal symptoms of the next attack appeared.

As already mentioned, these fevers could be modified by antipyretic drugs, such as acetylsalicylic acid and aminopyrine, but the attacks could not be thus prevented.

One measure which altered the time of occurrence of attacks was the induction of fever by the administration intravenously of killed typhoid organisms. The sharp febrile episode resulting from this was apparently identical with the attacks which occurred spontaneously. When such an artificial fever was induced on the eighth day after an attack, the next fever occurred ten days after the artificial one. This phenomenon has been repeatedly utilized by the patient to avert attacks which would normally fall on days on which he had some important job to do.

Statistical data on the distribution of attacks show that they had their onset most frequently at night, especially the severer ones. They occurred least often in the late afternoon. The interval between attacks lengthened when the patient was satisfactorily occupied and shortened when he was inactive, especially if under observation or hospitalized. Over all, the intervals between attacks became progressively shorter.

The fevers were not associated with loss of weight or debility, nor was there any evidence between attacks that the patient was ill. After five years of fevers appearing with increasing frequency he had his first remission. It was apparently spontaneous, and it lasted one hundred days. During this time his headaches, which had been suspended while he was having recurrent febrile attacks, recurred. Two years later he was admitted to the Mayo Clinic, where he was studied intensively. The only clue to the origin of the fevers was the finding of the same strain of alpha Streptococcus in his nasopharynx, tonsils and prostatic secretion. He was given a course of therapy with Rosenow's hyperimmune serum, from which he acquired serum sickness. After this his tonsils were removed, and subsequently his second remission occurred. This one lasted four and one-half months. The details of the history up to this time and the results of the studies at the Mayo Clinic are contained in Allen's paper.[14]

During the remission the patient began to suffer again from periodic headaches. With the recurrence of the fevers, however, the headaches once again stopped.

On March 8, 1940, the patient entered the Stanford University Hospital for study. The following data are supplied by Dr. Arthur L. Bloomfield. General

physical examination and examination of sensory and motor functions revealed nothing abnormal. Routine blood counts were normal except for the temporary leukocytosis which accompanied the bouts of fever. Blood cultures and agglutination reactions were negative for paratyphoid bacilli of types A and B, Salmonella suipestifer, Brucella abortus, Brucella melitensis and Brucella suis, as well as Bacillus tularensis. The agglutination test for typhoid organisms gave a positive reaction (*vide* numerous intravenous injections of killed typhoid organisms). The cutaneous reaction to coccidioidin was negative. Examinations of urine and feces, including repeated cultures, showed nothing abnormal. Culture of the prostatic secretion revealed 600 colonies of beta hemolytic Streptococcus per cubic centimeter. The Wassermann reactions of the blood and the spinal fluid were negative; the remainder of the examination of the spinal fluid revealed nothing abnormal. An electrocardiogram and an electroencephalogram were normal, as were roentgenograms of the skull and the chest and excretory pyelograms. The basal metabolic rate ranged between —1 and +15 per cent. Psychometric examination showed an intelligence quotient of 149. The erythrocyte sedimentation rate was repeatedly within normal limits.

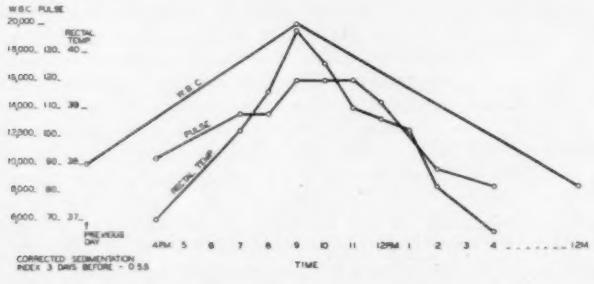
In the Stanford University Hospital, after the possibility of malingering had been carefully excluded, various therapeutic measures were undertaken without avail in an effort to eliminate the fevers, including administration of sulfanilamide, roentgen therapy over the cervical region and attempts at hypnosis. The latter failed because the patient resisted the procedure, unwilling to lose "an infinitesimal part of my will." One interesting finding came out of these studies, however. It was observed that vasomotor changes were associated with changes in the emotional state of the patient to the extent that it was possible to raise the cutaneous temperature of one extremity merely by suggestion. He was even able to accomplish this feat by autosuggestion. In such an attempt at autosuggestion later in the New York Hospital it was found that the cutaneous temperature of his right leg was raised 0.5 C. (0.9 F.) above that of his left leg as measured under basal conditions with a radiometer. The patient was discharged from Stanford University Hospital May 1. It was thought that the fevers resulted from an obscure infection, although the possibility of a neurogenic basis was entertained.

The patient was referred to the New York Hospital for further studies, with special attention to the mechanism of heat production. He was admitted on May 31, 1940 and studied in attacks much as he had been elsewhere. Since the likelihood of bacterial origin in the fevers had been pretty well excluded, more emphasis was placed on the possibility of virus origin. Accordingly, spinal fluid, blood and duodenal contents were collected during the height of fever and injected into mice and guinea pigs by Dr. Thomas P. Magill. Efforts thus to isolate a virus were unsuccessful. In view of the fact that the patient did not appear sick or debilitated in any way after twelve years of such vigorous illness it was held unlikely that his disease was infectious in nature. The figure illustrates the course of the rectal temperature and the pulse during a typical attack. The degree of leukocytosis is also recorded. Oral and axillary temperatures were also taken. The values were slightly lower than those of the rectal readings, as is usually found.

The relation of the bouts of fever to his "migraine" headaches was striking, particularly the fact that when the fevers started, the headaches to which he had been subject periodically ended, only to recur during the two periods of remission from the fevers. It seemed as if the two conditions were separately existing components of the same derangement. This relation suggested that the fevers might be due to a circulatory disturbance in the thermoregulatory centers. It is known that the headache of migraine is caused by excessive dilatation of chiefly extra-

cranial arteries of the head.[15] It is also known that in certain cases of migraine there occurs vasoconstriction of intracranial arteries, usually in the preheadache stage.[16] It was postulated that some such vasomotor derangement in the hypothalamus might be responsible for the febrile rises.

To test this possibility an attempt was made to abort febrile attacks by the administration of vasodilators, namely, glyceryl trinitrate and sodium nitrite. These drugs in doses of 0.0004 and 0.06 Gm., respectively, were administered at frequent intervals at the first appearance of prodromal symptoms. Two attacks appeared to have been aborted in this fashion, but eventually the fevers occurred despite the two compounds. Finally, the effect of sodium diphenylhydantoinate was tried. Accordingly, that drug was administered in doses of 0.1 Gm. four times a day. The patient had one more febrile attack two days after the institution of this therapy. In that attack, August 8, the rectal temperature rose to 39 C. (102.2 F.). From then on he was free of attacks until July 25, 1941. The apparent success of this drug, which is used almost exclusively in the treatment of epilepsy, suggested that this syndrome might be more closely related to "epilepsy" than to migraine. Sudden



Changes in the rectal temperature, pulse and number of white cells per cubic centimeter during a typical febrile attack.

withdrawal of the drug, however, after forty-four days of administration failed to induce an attack, although such a sudden withdrawal of anticonvulsant drugs is known to induce convulsive seizures in "epileptic" patients.[17] Other measures which are known to induce seizures in such persons were tried. The patient was kept awake for twenty-four hours, given exhausting mental, manual and physical work to do and fed alcoholic beverages throughout the twenty-four hour period, totaling in alcoholic content 120 cc. of 95 per cent ethyl alcohol. Later for a week his fluid intake was maintained in excess of 6,000 cc. daily. In the midst of this period he was given 1 cc. of solution of posterior pituitary U. S. P. intramuscularly. On the day of injection his urine output fell from 5,000 cc. to 2,500 cc.,

15. Graham, J. R., and Wolff, H. G.: Mechanism of Migraine Headache and Action of Ergotamine Tartrate, A. Research Nerv. & Ment. Dis., Proc. (1937) **18**: 638, 1938.

16. Schumacher, G. A., and Wolff, H. G.: Experimental Studies on Headache: B. Contrast of Vascular Mechanism in Preheadache and in Headache Phenomena of Migraine, Arch. Neurol. & Psychiat. **45**:199 (Feb.) 1941.

17. Dunning, H. S.: Convulsions Following Withdrawal of Sedative Medication, Internat. Clin. **3**:255, 1940.

indicating storage of fluid. None of these measures was successful in precipitating a febrile attack. The patient continued free of attacks without any further drug therapy.

The patient was subjected to a careful personality study. His family environment throughout childhood was rather rigid. His father was a strict, quiet and undemonstrative man. It has already been stated that he was subject to sick headaches and bouts of fever. His mother lay constant emphasis on culture and breeding. It was considered bad form at home to display any affection or other emotional reaction. He was conscientious and serious as a boy and extremely sensitive to the opinions of others, especially to disparaging remarks. His parents expected him to excel in his studies, and he did so, nearly always leading his classes. He entered college at the age of 17 but left in his third year to enlist in the Navy shortly before the United States declared war on Germany. He felt superior to other seamen and was distressed by their vulgar speech and manners. He soon earned for himself a commission as ensign, and later one as lieutenant. After the war he returned to college and in a year obtained a degree in engineering.

His past training and experience had inculcated in him high standards of performance, and the idea of failure was intolerable to him. Although he was a good engineer, he never became a business "success." He was unable to adjust his rigid personality to the "give and take" standards of the business world. He had a strict ethical code in business dealings, which in his opinion was frequently offended by unscrupulous tactics in general practice. He asserted, "I am incapable of in any way cultivating friendships with the thought that they may be useful to me in business." He felt insecure in the business world and anxious about his success. At the age of 25 he formed a company with two partners, but he resented strongly every instance in which his opinion was not able to prevail in business discussions. He admits that the venture might have succeeded "if I had been able to subjugate my opinions to those of my associates." The patient frantically redoubled his output of work in order to make his losing venture succeed. At this time he was tense, more anxious than ever and resentful that the whole onus had fallen on his shoulders. His periodic headaches became so severe as to be incapacitating, and it was necessary for him to quit work for a time.

Although he insisted on imposing his standards on other persons, it is interesting that in his personal relations he depended for emotional support on others, while he gave out comparatively little himself. "My friends assume a protective or paternal attitude that I don't particularly object to."

Six months after a disappointing love affair, when he was 27 years old, he met the woman whom he later married. They were both "given to critical analysis" and "sensed a kindredness of spirit." He passionately wished his marriage to be a perfect partnership, so he entered on it cautiously. He was especially anxious that neither his wife's nor his own "individuality" should be encroached on by the union. Accordingly, he drew up a contract which provided that each of them should be a free agent whose behavior was not to be hampered by the conventional restrictions of marriage. They deliberately undertook extramarital connections as "an expression of unhampered individuality to convince us that the verdancy of distant pastures may be somewhat illusory." Their experiences did not appear to affect his wife deeply one way or another. The patient, however, was offended by the experiences despite the fact that they had been at his own instigation. His first febrile episode followed his first extramarital experience, and his second, six weeks later, followed his wife's first experience. From that time on the patient became impotent in his relations with his wife. His general behavior became more compulsive than ever. He kept filed voluminous data and charts of events in his

illness, with meticulous attention to minutiae. The collection and classification of this mass of material became increasingly time-consuming and interfered with the accomplishment of his regular duties. He wrote daily letters to his wife on the typewriter and kept a carbon copy of each, meticulously filed away and clipped to the latest reply.

On examination the patient was alert and friendly. He seemed intensely interested in his illness but not much disturbed by it. He stated, "I have cultivated an impersonal attitude toward my illness." He frequently spoke in the third person or referred to himself as "we." In discussing his past life and personality reactions his manner was circumstantial and pedantic. He put undue stress on the selection of words and when discussing his status used involved medical terminology, at times sacrificing clear meaning for the use of intriguing words. He even occasionally concocted words. One was "frameria," which he said meant literacy and symmetry.

He expressed abnormal fears of large strange dogs, burglars, darkness, fire, bodily injury and a lingering illness. These had persisted since childhood. He avoided conflict with others, physical or mental. He was unhappy in controversial business discussions because he became "rattled and fearful and felt frustrated." Meticulous in his habits, he found it "impossible to slight work." After once undertaking a job he felt that he must carry it through at any cost. He was constantly obsessed by details of a problem and felt compelled to go over each one again and again.

The almost daily interviews necessary to elicit these data gave the patient an excellent opportunity for "mental catharsis." His illness was formulated to him as a functional disorder of the thermoregulatory apparatus in a setting of anxiety, insecurity and resentment precipitated by his two failures, business and marital. These failures were intolerable to him. He accepted this orientation and gained in time a good understanding of his condition. This, together with other less well defined factors, effected in him a marked improvement. At the time of discharge, he felt that his conflicts had been resolved to a large measure and he felt able to face his problems with more serenity. He accepted the inevitable fact that there were certain tasks which he could not do perfectly. In a letter written after he had been home and free of attacks for more than seven months he indicated that he had actually been able to face his life problems with less anxiety and conflict. He had found congenial work of a less intense type than that in which he had been engaged before he came to the hospital. He was employed in a consulting capacity by a large firm. He no longer had the interference of business partners to arouse resentment within him. He felt more secure both in his business and in his domestic relations, and fear of failure was no longer uppermost in his mind.

After a time, however, the work became gradually more intense, and during the phase of accelerated production for national defense the patient undertook the responsibility of designing a machine for the Army in a much shorter time than he was actually able to do. In this setting, after three hundred and fifty-one days free of fever, an anxiety tension state developed, and with it he had two bouts of fever similar to the old episodes. Whether this relapse will reestablish his rhythm of attacks or whether the bouts will constitute isolated occurrences is yet to be demonstrated.

COMMENT

It is unfortunate that the patients whose conditions were described in the literature on the subject of psychogenic fever were not subjected to detailed personality study, although in many instances they were

referred to as "neurotic" or "hysterical." Our patient has been studied carefully from the standpoint of the personality and found to fit into the reaction type characterized by obsessive and compulsive behavior. There was a family history of mental illness requiring hospital treatment on the maternal side and of migraine on the paternal side. His early home environment was rigid and uncompromising. His parents relentlessly demanded of him a high standard of performance. They would brook no failure. The patient himself was sensitive to slights, conscientious and insecure when without the approval of others. As a compensation for his essential passive nature with its dependency on others he assumed a kind of dominant attitude which showed itself in his pedantic behavior and in his inflexible life standards. While in school and college, when he had only himself and his books to reckon with, he led his classes and thus was able to feel secure with the approval of others. When he entered the business world, however, his inflexible attitude and rigidly systematized behavior proved a hindrance, and in consequent failures he experienced conflicts and feelings of insecurity. This was the period during which he was nearly incapacitated by his migraine headaches. When later he had to fit marriage into his rigid system of life, he found the task insurmountable. In this setting, during his early married life, the recurrent febrile attacks appeared.

The mechanism responsible for the fever is not clear, but it is possible that the attacks may be due to a vasomotor disturbance akin to that encountered in migraine.[18] This is suggested by the fact that the patient doubtless had migraine headaches and that these recurrent headaches were interrupted during the periods when he was suffering from recurrent fevers. Migraine is known to be a vasomotor disorder,[15] and furthermore, this patient has been shown to have vasomotor disturbances associated with changes in his emotional state by the fact that one can raise the cutaneous temperature of an extremity by suggestion. It is possible that a similar vasomotor change in the thermoregulatory apparatus may be responsible for his bouts of fever.

SUMMARY AND CONCLUSIONS

A case is presented in which the patient had suffered for many years with periodic sick headache and for thirteen years with frequently recurrent bouts of fever up to 40 C (104 F.). At intervals during this time he was hospitalized and carefully studied at three large institutions. An infectious, neoplastic or metabolic cause for his fever was never demonstrated, and indeed, the patient did not show loss of weight,

18. Wolff, H. G.: Personality Features and Reactions of Subjects with Migraine, Arch. Neurol. & Psychiat. **37**:895 (April) 1937.

debility or other evidence between attacks of being physically ill during or at the end of the thirteen years. Numerous therapeutic measures were ineffective in halting the attacks. After a personality study during which a great many personality disorders were uncovered, he was given an opportunity to ventilate his conflicts and some aid in resolving them. During this regimen his recurrent fevers stopped, and he had neither fever nor headache for nearly a year. Finally, while living in another part of the country where it was no longer possible for us to follow him up closely, the patient suffered a recurrence of his intermittent fevers. This occurred in a setting of unusual tension and anxiety. The fevers are believed to be due to a temporary derangement in the thermoregulatory centers of the brain, possibly of a vascular nature, arising in a setting of anxiety and insecurity in a rigid, compulsive person who has had migraine.

525 East Sixty-Eighth Street.

Progress in Internal Medicine

DISEASES OF THE HEART

A REVIEW OF SIGNIFICANT CONTRIBUTIONS MADE DURING 1941

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THE HEART IN WARTIME, WITH SPECIAL REFERENCE TO NEUROCIRCULATORY ASTHENIA

Nearly every one sensible of the war has felt its impact in some degree. Those within sight and sound of the shock of battle are affected most, but the rest do not escape. In addition to direct injury, disease and starvation, the increase in physical and psychologic stress and strain will most assuredly result in increased wear and tear on the body, including the cardiovascular system. The hours and the tempo of work will be increased, and older persons will forego, or will be called back from, retirement. There will be many causes and occasions for grief and anxiety. And the wholesale readjustment resulting from war will cause much concern.

Just how this will affect the incidence and aggravation of heart disease will never be known exactly. But already there have been many instances of the development of angina pectoris, congestive failure and myocardial infarction which are attributable to the war. Also of importance may perhaps be the hastening of degenerative processes, such as coronary atherosclerosis, which will eventually result in heart disease. Even if in the case of a single person the effect is slight, it assumes great importance when multiplied by the millions of persons involved. Compensations will probably result in that benefits will come from an increase in the knowledge of nutrition, traumatic heart disease and neurocirculatory asthenia, and the actual incidence of certain diseases associated with overnutrition, especially diabetes and hypertension, is likely to decline.

Neurocirculatory asthenia continues to be the most controversial wartime cardiac problem. There are some physicians who refuse to recognize it as a clinical syndrome. There are others who have found it wise to treat a patient with this condition as an ordinary medical

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patient suffering from fatigue without referring him either to a cardiologist or to a psychiatrist and in this way to avoid overemphasis either of the cardiac or of the mental state in the patient's mind. But by whatever name their condition is called and no matter what the emphasis, soldiers who display the symptoms commonly referred to as effort syndrome (England) or neurocirculatory asthenia (United States) constitute one of the important wartime medical problems. The small incidence of this disorder in the United States Army recruits is grossly misleading; potential cases are not recognized.

Wittkower, Rodger and Wilson [1] have made a careful study of 50 unselected soldiers aged 20 to 54 with clearcut effort syndrome. In their civil life 15 were sedentary workers and 35 were manual laborers. It is significant that no fewer than 29 had noticed their first symptoms in civil life, 10 during noncombatant service abroad, 4 after fighting experiences and 1 while in a hospital. After a thorough cardiologic investigation the patients were submitted to a three to six hour psychologic examination covering their whole life history.

Wittkower and his associates found that breathlessness was universally experienced and was the presenting symptom in 21 of their 50 patients and that dizziness, cardiac pain, palpitation, headache, nervousness, sleeplessness, undue sweating, tremor, fatigue while at rest, indigestion, nightmares, cramps, numbness, faintness, constipation and blurring of sight followed in that order. The chief cardiac symptoms, dyspnea, pain, palpitation and fatigue, were usually complained of only after the patient had made some slight effort, but in a few cases these symptoms were present when the patient was at rest.

As a result of the psychologic examination Wittkower and associates were enabled to detect a significant frequency of the following personality types:

Group 1. This group was made up of 20 men characterized by an unusually keen sense of duty and by a rigid and deep morality. As children, the majority had been serious minded, had worked rather than played in their spare time and had had an undue sense of obligation. They were obedient to the point of submissiveness, never told lies and felt unduly guilty about minor lapses. They were poor leaders, did not get into fights and were poorly poised. Nearly all were retarded in their sexual development and were shy in the presence of girls. In their occupations they were industrious and efficient, with perfectionistic tendencies. They avoided the minor indulgences of life; 12 of the 20 were teetotallers, 6 were moderate drinkers and only 1 drank excessively. They had little interest in sexual matters, and many were religious.

1. Wittkower, E.; Rodger, T. F., and Wilson, A. T. M.: Effort Syndrome, Lancet **1**:531, 1941.

Group 2. The 11 members of this group were similar to those in group 1 in their overconscientiousness but were more aggressive. Most of them had had an unhappy childhood. Feelings of inferiority were often concealed by a strong desire for independence, by overweening ambition or by a compensatory self-assertive, self-righteous attitude. Later in life their ambitious drive qualified them as efficient workers, but when faced with frustration, they tended to be resigned grousers rather than open rebels.

Group 3. This group comprised 3 men whose lifelong aggressiveness had arisen in childhood under circumstances similar to those which had produced the grousing resentment of the men in group 2. They were open rebels and had repeatedly been in trouble.

Group 4. This group consisted of 12 men with inferior physique combined with emotional and instinctual immaturity. They were delicate as children, and 8 of the 12 were unfit for games. They sought protection rather than fight their own battles. Their feelings of inadequacy made them shy and retiring. They put forth considerable effort in their occupations but often failed. On joining the service they suffered unduly from the separation from family and often broke down during training.

Group 5. This consisted of a well defined group of 4 soldiers who lacked the severe sense of duty found in the others and who were described as "quitters." They were physically and psychologically inferior and had "apparently given up the struggle for existence before it had properly started."

Wittkower and his associates then considered the predisposing and precipitating factors. They found evidence of life-long physical inferiority in 15 of the 50 patients, and 18 gave a long history of nervousness and of breakdown prior to the onset of effort syndrome characterized by anxiety, restlessness and severe phobias. Possible precipitating factors were found to be emotional strain (34), physical strain (23), febrile illness (21), abuse of nicotine (5), accident (4) and gas poisoning (1). An analysis of the various types of acute or chronic emotional disturbances (in 34 of the 50 patients) showed marked variation in the five personality groups. With respect to causation the fundamental importance of emotional factors is stressed, but the authors point out that this would be incomplete unless the various other factors encountered were taken into account. They illustrate the difficult and complex nature of the causation of effort syndrome with 2 case reports. They conclude that the only constant factor in determining the occurrence of effort syndrome is the preexistence of a "character" disorder, and among the precipitating factors emotional disturbances were the commonest.

Wittkower, Rodger and Wilson's contribution was intended "to assess the relative significance of the various etiological factors encountered." This assessment was made. That they "encountered" all of the significant etiologic factors cannot be proved, and the authors express themselves cautiously with respect to causation and stress its complex nature. Some of the uncertainty rests in the fact that it is difficult to prove the correctness of a psychiatric opinion. Psychiatrists readily discover character disorders; they seem quick to regard as expressions of abnormality those very traits which have so long been considered virtues. It seems to us that the five groups can be broken down into two main groups with three subdivisions in the first and two in the second. It is not surprising that Wittkower and his associates found none of their 50 patients to be emotionally well adjusted, and this fact alone cannot be used to prove a common causation of the effort syndrome. On the other hand, it does appear that the symptoms in some, if not a majority, of their particular patients could best be explained on the basis of emotional factors. It is probable that their group of patients does not represent the total experience of this disorder.

Jones and Lewis [2] have reported an interesting study on more than 200 soldiers who were admitted to an emergency hospital during a twelve month period with conditions given the diagnosis of effort syndrome. In their own words,

> The inquiry has been directed to the phenomena; the mechanisms at work in producing them; the external (environmental) causes, remote or recent, which have set these mechanisms in action; and the internal (constitutional) causes which have enabled external causes to act thus. Prognosis and treatment have also been considered. Physiological and psychological data, collected in the course of a more restricted and detailed investigation, are not included here.

In discussing the "phenomena" Jones and Lewis point out that the physical phenomena of effort syndrome have often been fully described and that they have nothing to add, but that the subjective or obviously psychologic phenomena have received little attention. They inquired into the mood and outlook in each of their patients and found that 76 per cent had conscious fear accompanying their symptoms at times and that 72 per cent had attacks while at rest corresponding to the familiar anxiety attack. They found that hypochondriacal phenomena were not uncommon. Fifty-three per cent of the patients were unduly preoccupied with their symptoms, and 64 per cent expressed the belief that they had some disease of the heart.

The authors state:

> The mechanisms can be seen physiologically as those of the autonomic system, psychologically as those of emotional expression; this familiar dualist attitude is

2. Jones, M., and Lewis, A.: Effort Syndrome, Lancet **1**:813, 1941.

pragmatically justifiable, though the two types or mechanisms can more properly be regarded as two aspects of the same complex happening, each capable of more or less separate and independent activation. Thus fear, as a subjective experience, will as a rule be accompanied by somatic (autonomic) manifestations—sweating, goose-flesh and dry mouth—but fear may be experienced without these physical signs, and some at any rate of these physical signs may be exhibited (for instance, under the influence of drugs) without the subject feeling the same quality of emotion. As to their prevailing mood, 50% of the men were depressed and over 70% showed evidence of anxiety. . . .

It is difficult to describe the psychological mechanisms (as apart from the causes) whereby symptoms are produced. A mechanism implies a fixity of performance, no matter how it is set going or where it is occurring, which is difficult to distinguish in the details of individual psychological behaviour, the nearest approach to it being evident in the development of habits, or so-called complex conditioning. There are at present several psychological theories—for example, the Pavlov theory of conditioned reflexes and the various hormic and libidinal theories of dynamic psychology—in terms of which the mechanism of symptom formation in these patients can be described, but such alternative explanations, equally plausible and equally disputable, are rightly suspect.

There is, moreover, no such regularity in the psychological as in the physical phenomena, since by definition certain physiological phenomena, such as breathlessness, must be present, and the physical apparatus subserving these phenomena must therefore be in action, whereas there is no word of explicit psychological phenomena in the definition. Consequently the term includes patients with anxiety and depression of which they are aware, as well as those who are not conscious of any such feeling; patients who are hysterically keeping up and fostering their symptoms, along with others who hypochondriacally fear theirs; some whose symptoms are physiogenic, as after severe influenza; and some who have no symptoms that cannot be interpreted as plain fright. There is a constant temptation to single out one of these groups and call it true effort syndrome. Acually the problem is not that of effort syndrome but of anxiety neurosis, hysteria, hypochondriasis, post-influenzal fatigue and other states which are all lumped together under this umbrella; and the mechanism is as little or as much known as the pathology of these familiar conditions. We have not found anything peculiar to effort syndrome in the psychopathology of the cases seen here. Studies of the inter-relation of the psychological and physiological phenomena are more to the point, as are studies of the psychological aspect of causation, next to be discussed.

Jones and Lewis then turn to a discussion of external and internal causes. Among the immediate external causes (army life) work or effort was less significant than they had expected it to be. Only 47 per cent of the entire group reported that the work they were doing when their symptoms began was heavier than that to which they were accustomed. Other immediate factors were exhaustion, infection, lack of sleep, separation from family, financial worries, etc. Almost equally important were remote external causes, such as psychologic traumas in childhood and parents with similar symptoms. With respect to internal causes the authors found that soldiers with effort syndrome are not, as a group, more asthenic in build than healthy soldiers and that they have a normal distribution of intelligence. However, they found a study of "function"

more enlightening. Fifty per cent of their patients had symptoms of vegetative disorder, such as breathlessness, palpitation, excessive sweating or diarrhea on slight provocation of an emotional sort. Thirty-eight per cent found it difficult or impossible to wear a gas mask, as it made them feel they were choking and breathless. Forty per cent had not played any games, and only 25 per cent had fairly good athletic records. Half of the men had shown definite neurotic traits and two thirds a more or less pronounced anomaly of personality. In discussing the nature of the disorder, Jones and Lewis state:

> The evidence is that effort syndrome is not a homogeneous group from any clinical standpoint, though administratively and practically there are excellent reasons for delimiting it. The syndrome is, however, in its setting, causes and form, a neurotic one. This is not to say that it is mainly a psychogenic disorder. Neurosis, like all mental disorders, can be in considerable measure physiogenic (as postencephalitic obsessional neurosis, postinfective neurasthenia and post-concussional personality disorder illustrate), but it does have to exhibit disturbances of function at a high level of integration—i. e., psychological disturbances—and its symptoms must not be such as can be properly attributed to definite and recognisable organic disease. In this sense effort syndrome is a neurosis. Such a classification does not prejudge the issue of what physiological mechanisms are at work nor indicate that psychological treatment is necessarily called for in all cases. A neurosis is a disorder of the patient, not of his disembodied mind only, or of his mindless body only, if such things can be conceived of. In a neurosis, physiological phenomena, either constitutional or temporary and reversible, will occur along with more conspicuous psychological ones. This is true of all illnesses that can be classified as mental disorders, of whatever degree or type—neuroses and psychoses, physiogenic and psychogenic. The distinction is only one of convenience at bottom.
>
> We have therefore not been satisfied with effort syndrome as a diagnosis, but have classified the cases (100 successive admissions) as follows: anxiety state, acute 17%, chronic 14%; depression 12%; psychopathic personality 18%; hysteria 11%; postinfective 11%; hyperventilation tetany 1%; organic disease 11%; high-grade mental defect 4%; schizophrenia 1%.

Treatment consisted of graduated exercises, systematic occupation and psychotherapy. The last-named treatment was not different from that given to other neurotic patients. The prognosis for the group was only fairly good. About 20 per cent of the patients were apparently cured and returned to the army for full duty; a similar percentage were discharged from the army as unfit. The remaining 60 per cent were returned to the army for light duty. A follow-up study of a large sample of those returned to the army revealed that a third did well, a quarter did moderately well and the remainder had to be discharged as unfit.

Jones and Lewis agree in a broad way with Wittkower and associates that effort syndrome is essentially a mental disorder. This conclusion certainly seems justified from the data they present. This does not remove the possibility that a more adequate explanation for the symptomatology of effort may be found.

Wood [3] has approached the problem of neurocirculatory asthenia (or Da Costa's syndrome, the term for which he states a preference) from a somewhat different point of view than Wittkower and associates [1] and Jones and Lewis [2] but has reached the same general conclusion after close personal contact with 300 patients.

He immediately challenges the observation of Lewis that the symptoms are often no more than exaggerated manifestations of the healthy responses to effort. He compares the symptoms as found in 200 of his patients with those in 50 healthy subjects after exercise and concludes that a different mechanism probably determines the symptoms in the two instances. On the other hand, a comparison of the symptoms and signs of Da Costa's syndrome with those produced in normal persons by some of the unpleasant emotions or in patients with psychoneurosis reveals a great similarity.

Wood then reports his critical observations on the mechanism of the somatic manifestations and attempts to show that the chief symptoms and signs of Da Costa's syndrome are directly or indirectly the result of a neurosis and are not the expressions of an abnormal physiologic response to effort.

A careful study was made of the cause and site of origin of the pain in the chest in selected patients. It was shown that tenderness and pain in 11 patients was abolished after the local injection of procaine hydrochloride into the intercostal muscle. Cutaneous anesthesia was never obtained, showing that the intercostal nerve was not blocked. It was logically concluded that the pain was of local origin and not referred from the heart or elsewhere. It was further shown that inframammary pain on the left side was usually associated with poor movements of the diaphragm and with poor thoracic expansion and that sometimes it was obviously the result of muscular strain. Wood concludes this section as follows:

> Left inframammary pain arises in local muscular or fibrous tissue; it may be due to fatigue or strain of certain muscular attachments involved in such actions as cranking a lorry or lifting a heavy weight; to incessant minimum trauma from the overacting heart of cardiac neurosis; it is predisposed to by poor physique in Da Costa's syndrome; it is maintained and exaggerated by the belief that it arises in the heart. Several of these factors may operate together.

Other signs and symptoms were analyzed in a similar fashion, and evidence is given in support of the contention that they are chiefly related to anxiety. Of particular interest is the discussion of breathlessness and hyperventilation. Wood believes that the most probable

3. Wood, P.: Da Costa's Syndrome (or Effort Syndrome), Brit. M. J. **1**: 767 and 806, 1941; Aetiology of Da Costa's Syndrome, ibid. **1**:845, 1941.

explanation is that the stimulus is emotional. With regard to the "hyperventilation theory" he concludes:

> The total evidence indicates that hyperventilation cannot be held responsible for the symptoms and signs of Da Costa's syndrome, neither by causing tissue alkalosis nor by interfering with the circulation; but, apart from rare organic causes, merely one mechanism by which psychosomatic manifestations are produced. It is commonest in the hysteric.

Thus Wood, having reached the conclusion that the signs and symptoms of Da Costa's syndrome are produced by central stimulation, turns to a consideration of the real nature of the disorder, namely, the origin of the central stimulation. By careful analysis of case histories he shows that the central stimulus is emotional and is commonly the result of fear. He states:

> The reaction becomes linked to effort by a variety of devices, which include misinterpretation of emotional symptoms, certain vicious circular patterns, the growth of a conviction that the heart is to blame, consequent fear of sudden death on exertion, conditioning, and hysteria.

Wood finally urges that the diagnosis of "effort syndrome" be dropped, as a proper psychiatric diagnosis is nearly always available.

In our opinion Wood's paper is likely to stand out as one of the most important contributions on the disorder which we now call effort syndrome or neurocirculatory asthenia. This is not so much because of his statement that it is a functional disorder—most observers are already of this opinion—but because he has given good proof for this belief and has pointed out a plausible mechanism. There is little doubt that his interpretation is the correct one for a majority of cases, and it is supported by the findings of Wittkower and associates [1] and of Jones and Wilson,[2] who share the same general opinion.

Parkinson [4] discusses effort syndrome from a more general standpoint. He fully appreciates the importance of the emotional factors but warns against too readily accepting the opinion that it is simply a psychoneurosis and says:

> It is not certain how far this definition will carry us, because the term can be so readily applied to any form of ill-health which is imperfectly understood and unaccompanied by organic signs. After all, psychological variations and faults in healthy people are common enough. It could only be a bar to medical progress if psychoneurosis (or psychosomatic disease) remained a label and became a dumping-ground for most unexplained illness, much as did "neurasthenia" in the past. It is still to be decided how far psychotherapy is rational and effective treatment; besides, an explanation for the predominance of circulatory symptoms, the relation of effort, and the relative uniformity of the clinical picture is not yet forthcoming. Certainly the time is ripe not only for psychological but for other investigations, as it would appear that autonomic nervous, endocrine, respiratory,

4. Parkinson, J.: Effort Syndrome in Soldiers, Brit. M. J. **1**:545, 1941.

and metabolic factors may also operate in effort syndrome, and will also engage the attention of the physician seeking a wider conception of its essential features. Doubtless this expanded approach has much to commend it, and will deepen and broaden our vision of what is at present obscure in the rationale of effort syndrome.

White [5] has discussed the problem of heart disease in soldiers. He first traces the development of present knowledge in this regard and points out that a considerable advance has been made in the last two decades in three important respects: (1) the rejection as new recruits of men with important cardiovascular lesions; (2) the early recognition of disabling cardiac conditions in the Army itself, and (3) the adoption of measures to protect soldiers from some of the causes of heart disease, particularly syphilis and rheumatism.

In discussing the problems concerning the soldier and his heart for the future he states:

> In the first place, physicians must try to hold the great gains that have been made in the last generation; this is not hard to do in time of peace but undoubtedly more difficult under the stress and strain of rapid mobilization and war, when large numbers of new recruits must be examined and enlisted. Some preparedness can be effected by careful universal periodic examination of the male population of military age in time of peace. This doubtless will some day be a routine public and private health measure.
>
> The important specific problems are: first, to learn far better than is now known the range of the normal heart as to size, sounds, action, roentgen picture and electrocardiogram; second, to decide what minor abnormalities may be safely passed for military service; third, to detect at their very beginning lesions of the heart and aorta, especially acute rheumatism and syphilitic aortitis; fourth, to decide what newly acquired lesions or symptoms and signs are compatible with military life and in what capacity, and, finally, to study further the two chief problems of the army of the present day which are associated with cardiac lesions or symptoms, namely, coronary disease and severe neurocirculatory asthenia, in order to try to prevent or to minimize these conditions or at least to recognize them early, so that they may be avoided in new recruits or made a basis for discharge for disability of soldiers already in service.

PHYSIOLOGY OF RESPIRATION

The functions of the circulatory and the respiratory system are so intimately connected that a brief summary of certain of the recent advances in respiratory physiology seems not out of place here. Some of the newer observations are of great practical significance and have not yet been brought sufficiently to the attention of those engaged in the clinical practice of medicine. For a fuller description than is here given the reader is referred to Schmidt and Comroe's excellent review.[6]

5. White, P. D.: The Soldier and His Heart, War Med. **1**:158 (March) 1941.

6. Schmidt, C. F., and Comroe, J. H., Jr.: Respiration, in Luck, J. M., and Hall, V. E.: Annual Review of Physiology, Stanford University, Calif., Annual Reviews, Inc., 1941, vol. 3, p. 151.

The physiology of respiration is logically divided into "external" and "internal" respiration. The remarks which follow are chiefly concerned with external respiration, which deals with the interchange of gases between the atmosphere and the lung and between the lung and the blood. Internal respiration deals more intimately with the actual process of tissue respiration.

Breathing is the most important physiologic function, under both voluntary and involuntary control. Ordinarily, it is not a wilful act but is regulated automatically through reflex and chemical channels, in accordance with the metabolic requirements of the body. Breathing is normally adjusted to maintain a fairly constant composition of the alveolar air, and it is alveolar air and not atmospheric air with which the body remains in gaseous equilibrium. Alveolar air contains approximately 14 per cent oxygen and 6 per cent carbon dioxide. If the respirations are abnormally depressed, the percentage of oxygen in alveolar air decreases and the percentage of carbon dioxide increases, both changes being undesirable. If the respirations are abnormally increased (hyperventilation), the percentage of oxygen increases, which is not undesirable, but the decrease in carbon dioxide may provoke undesirable symptoms.

The Respiratory Center.—It has long been customary to think of the respiratory center as a small discrete structure located in the medulla. However, the evidence cited by Schmidt and Comroe [6] makes it seem certain that instead of a compact center there are many inspiratory and expiratory "spots" [7] scattered bilaterally in the gray matter of the ventral reticular formation of the medulla overlying the upper four fifths of the inferior olive and probably an additional expiratory "center" in the upper part of the pons.

Normal rhythmic respiration probably depends on periodic inhibition of the inspiratory neurons by nerve impulses aroused by the inspiratory act. There is not entire agreement with regard to the reciprocal innervation between the inspiratory and the expiratory neurons, but the former are apparently inhibited either by efferent impulses from the expiratory center in the pons or by afferent impulses carried by the vagi.

In discussing the interrelations of chemical and reflex stimuli in the adjustments of the pulmonary ventilation, Schmidt and Comroe emphasize the dominance of the reflex factor and state that in their opinion

> . . . the time has come to reverse the traditional attitude and to look upon the changes in the chemical stimulus in the blood occurring under ordinary physiological as well as most pathological conditions as results rather than causes of changes in pulmonary ventilation.

7. Pitts, R. F.: The Differentiation of Respiratory Centers, Am. J. Physiol. **134**:192, 1941.

With respect to chemical stimuli there is increasing evidence that normally carbon dioxide is the chief, if not the only, chemical stimulus to the center controlling respiration. It is doubtful if changes in p_H have a direct effect on the center.

Respiratory reflexes may arise as a result of pressure changes in the carotid sinus and aortic arch and, what is more important, as a result of stimulation of the chemoreceptors in the carotid and aortic bodies. There is evidence that the chemoreceptors are not an important factor in the control of normal respiration by carbon dioxide because the respiratory center is much more sensitive to carbon dioxide. However, change in p_H, anoxemia and certain drugs act as relatively strong stimulants to the chemoreceptors, and their action on the center is weak or even depressant.

Some Clinical Considerations.—Muscular Exercise: The increase in respiration as a result of muscular exercise has usually been regarded as being due either to increased chemical stimulation of the respiratory center or to an increased sensitivity (to chemical stimuli) of the center. Recent observations, especially those of Neilsen,[8] have convincingly shown that the hyperpnea of muscular exercise is far greater than it should be if it were due to an increase in carbon dioxide, change in p_H or lowered arterial oxygen saturation. The inference to be made is that some reflex factor is concerned, and there is some evidence that such reflexes do exist and that they probably arise from the muscles and lungs.

The Dyspnea of Heart Failure: Much the same type of experimental evidence, as was already mentioned with reference to muscular exercise, has led to the conclusion that the dyspnea associated with heart failure is largely due to reflex stimulation resulting from congestion of blood in the pulmonary circuit. However, in some instances at least, the decrease in cardiac output and the decrease in cerebral blood flow are important factors.

The Hyperpnea of Anoxemia: This has been clearly shown to be due to reflex stimulation by way of the chemoreceptors in the carotid and aortic bodies. Moderate oxygen lack has practically no effect on the respiratory center and with greater lack the activity of this center is depressed, not stimulated. On the contrary, anoxemia acts as a strong stimulant to the chemoreceptors, and respiration is greatly augmented through a reflex mechanism. A depressant action is not observed until a profound degree of anoxemia is reached.

Cheyne-Stokes Respiration: This phenomenon is usually associated with conditions causing depression of the respiratory center, but the

8. Nielsen, M.: Die Respirationsarbeit bei Körperruhe und bei Muskelarbeit, Skandinav. Arch. f. Physiol. **74**:299, 1936.

stimulant action of anoxemia on the peripheral chemoreceptors persists and contributes in an important way. Thus, when respirations are decreased or abolished as a result of depression of the respiratory center, the arterial oxygen saturation falls. Despite some degree of depression of the chemoreceptors, the oxygen lack finally becomes a sufficiently powerful stimulus and respiration is reflexly increased. This serves to increase the arterial oxygen saturation until the degree of anoxemia is no longer sufficient to stimulate the chemoreceptors and apnea results. Thus one cycle is completed, and another cycle of alternate hyperpnea and dyspnea begins.

Anesthesia and Depression of the Respiratory Center: A few years ago Marshall and Rosenfeld [9] pointed out that if the respiratory center was sufficiently depressed in animals as a result of barbiturate anesthesia, respirations might be maintained by the stimulant action of anoxemia on the chemoreceptors in the carotid and aortic bodies, and if conditions were just right, the administration of oxygen would reduce the stimulus and lead to respiratory arrest. That this may be the mechanism of certain deaths in human beings is likely. Beecher and Moyer [10] in their studies on the mechanisms of respiratory failure in dogs under evipal sodium (sodium C-C-cyclohexyenyl-N-methylbarbiturate) and pentothal sodium anesthesia have also shown that over a wide range of anesthesia oxygen lack (anoxemia) causes a great increase in pulmonary ventilation. This is due entirely to stimulation via the carotid and aortic bodies, which tends to mask the depression of the respiratory center. Under these circumstances, if the arterial oxygen saturation is sufficiently increased, the carotid and aortic bodies are no longer adequately stimulated. Respirations are slowed, and carbon dioxide is allowed to accumulate in the blood and tissues. The center has lost much of its ability to respond to carbon dioxide and will be further depressed by high concentrations. Respirations finally fail. The clinical implications are obvious, with respect both to the judgment needed in using barbiturates as anesthetics and to the danger of increasing the oxygen concentration of the inspired air when the respiratory center has been depressed.

Carbon Monoxide Poisoning: A comparison of the effects of acute carbon monoxide poisoning and anoxemia in human beings [11] affords

9. Marshall, E. K., Jr., and Rosenfeld, M.: Depression of Respiration by Oxygen, J. Pharmacol. & Exper. Therap. **57**:437, 1936.

10. Beecher, H. K., and Moyer, C. A.: Mechanisms of Respiratory Failure Under Barbiturate Anesthesia (Evipal, Pentothal), J. Clin. Investigation **20**:549, 1941.

11. (*a*) Asmussen, E., and Chiodi, H.: The Effect of Hypoxemia on Ventilation and Circulation in Man, Am. J. Physiol. **132**:426, 1941. (*b*) Chiodi, H.; Dill, D. B.; Consolazio, F., and Horvath, S. M.: Respiratory and Circulatory Responses to Acute Carbon Monoxide Poisoning, ibid. **134**:683, 1941.

considerable insight into the factors controlling respiration and circulation. It is shown that there is a markedly different respiratory and circulatory response to the two forms of hypoxemia even when the available oxygen in the arterial blood is the same. The reason for this is that the carotid and aortic bodies are stimulated by a decrease in oxygen tension of the arterial blood and not by a decrease in oxygen content, at least of moderate degree. In acute carbon monoxide poisoning, the oxygen content of the arterial blood is reduced but the tension is relatively little affected. In this circumstance hyperventilation does not occur; the cardiac output is not increased, but the pulse rate is raised. On the other hand, anoxemia resulting from oxygen lack decreases the oxygen tension as well as the content of the arterial blood. This leads to hyperventilation, an increase in cardiac output and an increase in pulse rate.

Carbon Dioxide Transportation: The absorption of carbon dioxide by the blood in the tissues and its evolution in the lungs proceeds at a much faster rate (seventy-five-fold) than would be true according to the speeds of uncatalyzed chemical reactions involved. The limiting factor (i. e., the slowest step) is the reaction $CO_2+H_2O \rightleftarrows H_2CO_3$, and it has been shown that this is greatly hastened by the enzyme "carbonic anhydrase." Now it has recently been shown [12] that sulfanilamide strongly inhibits the action of this enzyme, and the question arose as to whether this drug would lead to retention of carbon dioxide and its consequent serious disturbances. The danger however, is apparent only in exhaustive exercise,[13] chiefly because the available amount of carbonic anhydrase is many times that of body needs and also because a part of the carbon dioxide transported will rapidly combine with hemoglobin (forming carbhemoglobin) with the aid of a catalyst.

THE MEASUREMENT OF BLOOD PRESSURE

Recent studies, previously reviewed,[14] on the range of normal blood pressure led to the conclusion that the upper limit is around 120 mm. of mercury systolic and 80 mm. diastolic and the normal fluctuations, determined by repeated observations, are usually not over 10 mm. It was further stated that the lower limit of normal blood pressure is around 90 mm. systolic and 55 mm. diastolic. The commonly accepted

12. Mann, T., and Keilin, D.: Sulphanilamide as Specific Inhibitor of Carbonic Anhydrase, Nature, London **146**:164, 1940.

13. Roughton, F. J. W.; Dill, D. B.; Darling, R. C.; Graybiel, A.; Knehr, C. A., and Talbott, J. H.: Some Effects of Sulfanilamide on Man at Rest and During Exercise, Am. J. Physiol. **135**:77, 1941.

14. Graybiel, A., and White, P. D.: Diseases of the Heart: A Review of Significant Contributions Made During 1939, Arch. Int. Med. **65**:1053 (May) 1940.

view of a positive relation between hypertension and body build has also been statistically confirmed; thus, in a random group of hypertensive subjects there will be nearly three times as many who are overweight as ones who are underweight. The recent trend has been, therefore, to revise downward the criteria for normal blood pressures and to narrow the borderland between the normal and the abnormal. The recent recommendations of the American Heart Association with regard to the technic of blood pressure determination were made with the hope that by standardizing the instruments and the technic, the difference in measurement among examinees would be reduced.

This whole question of greater accuracy in the determination of blood pressure and the sharper definition of normal blood pressure gives particular point and application to the observations of Rogan and Bardley.[15] They undertook to test the accuracy of clinical measurements of blood pressure by a comparison of readings obtained simultaneously by direct (intra-arterial) and indirect (auscultatory) measurement.

With respect to systolic pressure Rogan and Bardley found that the agreement between the direct and the indirect measurement was affected both by the size of the subject's arm and by the contour of the pulse wave. They found that when the pulse wave was of an "empty, peaked" type, the auscultatory reading tended to be too low, whereas with a relatively full pulse there was good agreement between intra-arterial and auscultatory readings. Much more important, however, was the size of the arm. The auscultatory measurements of systolic pressure are usually too low in subjects with small arms and too high in subjects with large arms. In occasional subjects they found the auscultatory measurements to be grossly inaccurate (30 mm. above or below the intra-arterial pressure), but when the subjects with aortic insufficiency and those with upper arms greater than 35 cm. or less than 24 cm. in circumference were excluded, the auscultatory readings were within ± 10 mm. of the intra-arterial pressure in 83 per cent of the comparisons. From this they conclude that false diagnoses of arterial hypertension are likely to be made in large or obese persons and false diagnoses of hypotension only in small or emaciated persons. In some obese subjects it was found that the substitution of a wide (20 cm.) blood pressure cuff for the standard (13 cm.) cuff afforded more accurate auscultatory measurements both of systolic and of diastolic pressure, but in most subjects the wide cuff yielded measurements which were too low.

With respect to diastolic pressure the auscultatory estimates were found to be usually too high, the mean deviation being $+8$ mm. of mer-

15. Rogan, C., and Bardley, J., III: The Accuracy of Clinical Measurements of Arterial Blood Pressure, with a Note on the Auscultatory Gap, Bull. Johns Hopkins Hosp. **69**:504, 1941.

cury in 101 comparisons (excluding the subjects with aortic insufficiency). The positive deviation increased with increasing size of arm and was of an order of approximately 3 mm. for each 1 cm. increase in arm circumference. As was to be expected in some instances of aortic regurgitation, the auscultatory measurement of diastolic pressure was much too low.

AUSCULTATION

Rappaport and Sprague [16] have presented an important analysis of the characteristics of human hearing which are related to auscultation. This material is followed by a description of cardiac sounds, murmurs and noncardiac chest sounds from a physical point of view. A theoretic analysis of the action of the acoustic stethoscope and various chest pieces (open bell and diaphragm bell types) is made and verified by experiment. For practical purposes it is shown that in auscultating the heart both an open bell and a diaphragm bell may be used to advantage. They point out that the important consideration with respect to the open bell is to keep its internal volume at a minimum and have it so shaped that it will not too readily fill with flesh when applied to a patient's chest. In the case of the diaphragm bell the air space should be small in order to obtain maximum efficiency. The tubing should be as short as possible.

An instrument is also described (including the underlying theoretic principles) which is capable of amplifying the auscultatory sounds without altering their character and which simultaneously registers a phonocardiogram, an electrocardiogram and a sphygmogram.

The authors show that when a patient is auscultated by the usual stethoscope, the observer definitely does not hear the cardiac sound vibrations as they actually exist at the source, because of three major forms of modification, namely:

1. The heart sounds are modified in their path of travel from the source to the surface of the chest by intervening tissue.

2. The vibrations that reach the surface of the chest are further modified by the stethoscope and the type of chest piece employed.

3. The human hearing mechanism (that is, the ear, the nervous pathways and the brain) additionally modifies the heart sound vibrations.

The study of acoustics as related to auscultation, therefore, deals with the vibrations or disturbances set up in the chest and their transmission through the structures of the chest, as well as through the stethoscope—with resulting auditory perceptions.

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16. Rappaport, M. B., and Sprague, H. B.: Physiologic and Physical Laws That Govern Auscultation, and Their Clinical Application, Am. Heart J. **21**:257, 1941.

In phonocardiography certain standards must be decided on and faithfully adhered to. The authors have suggested phonocardiographic standards based directly on the stages of sound modification encountered in ordinary auscultation. Thus, three distinct types of phonocardiographic registration are considered: linear, stethoscopic and logarithmic.

Linear phonocardiography registers graphically the mechanical vibrations set up by cardiac action as they exist on the surface of the patient's chest—that is, the deviation of the recording galvanometer beam is proportional to the intensity of the vibration at the surface of the chest. The stethoscopic system of phonocardiographic registration does not register the cardiac sound vibrations as they exist on the surface of the patient's chest but as they are presented to the ears of an observer by an average acoustic stethoscope. The logarithmic phonocardiogram is a graphic representation of the cardiac sound vibrations as they are actually heard or perceived by an average observer of normal hearing when an average acoustic stethoscope is used. That is, the modifications of the stethoscope plus those of human hearing are taken into consideration.

According to the authors, an acceptable phonocardiographic instrument must be capable of linear, stethoscopic and logarithmic registration, as each system supplies certain information which the others cannot supply. An understanding by a physician of the underlying phonocardiographic principles described in this investigation is also considered by the authors to be essential to the interpretation of phonocardiograms.

ELECTROCARDIOGRAPHY

Hoff and Nahum and their associates [17] have reported their interesting observations on the genesis of the normal and the abnormal electrocardiogram in experimental animals. They obtained curves after cooling and warming the heart and after extinguishing electrical activity over various portions of the epicardium by means of potassium chloride.

They found that curves obtained after extinction of the electrical activity over one ventricle resembled those derived directly from the surface of the other ventricle. Such curves were called dextrocardiograms and levocardiograms. The dextrocardiogram is mainly upright in the three limb leads, and the levocardiogram is mainly inverted. The

17. (*a*) Nahum, L. H.; Hoff, H. E., and Kaufman, W.: Formation of the R Complex of the Electrocardiogram, Am. J. Physiol. **134**:384, 1941; (*b*) The Nature of Leads I and III of the Electrocardiogram, ibid. **134**:390, 1941; (*c*) Configuration of Anterior and Posterior Septal Extrasystoles in the Standard Leads of the Electrocardiogram, ibid. **134**:398, 1941; (*d*) Influence of Right and Left Ventricles on the Electrocardiogram, ibid. **131**:687, 1941; (*e*) The Significance of Displacement of the RS-T Segment, ibid. **131**:693, 1941. (*f*) Hoff, H. E., and Nahum, L. H.: The Factors Determining the Direction of the T Wave: The Effect of Heat and Cold upon the Dextro- and Levocardiogram, ibid. **131**:700, 1941.

electrocardiogram was found to be the algebraic sum of the dextrocardiogram and the levocardiogram.

It was observed that when the left ventricle alone was injured dextrocardiograms were always obtained and the RS-T segments were elevated in each lead and when the right ventricle was injured only levocardiograms were obtained, with the RS-T segments depressed in all leads. In each instance the greatest displacement of the RS-T interval would be in lead II, because lead II is the algebraic sum of leads I and III. However, when the anterior surface of the heart was injured, thus involving both the right and the left ventricle, the RS-T segment was elevated in lead I (posterior dextrocardiogram) and depressed in lead III (posterior levocardiogram). When the posterior surface of the heart (apex and posterior septal region) was injured, the RS-T interval was depressed in lead I (anterior levocardiogram) and elevated in lead III (anterior dextrocardiogram). In addition to the clinical implications, these results suggested that in the normal heart lead I represents chiefly the interference between the action potentials of the anterior surface of the left verticle (anterior levocardiogram) and the posterior surface of the right ventricle (posterior dextrocardiogram) and that lead III represents the algebraic sum of the anterior dextrocardiogram and the posterior levocardiogram. Lead II appears to record from the entire heart. This conclusion was supported by studies on the T waves, R waves and extrasystoles now to be described.

Hoff and Nahum and associates found that heating and cooling the right or the left ventricles shortened or lengthened, respectively, the dextrocardiogram or the levocardiogram. They observed that in the dog the dextrocardiogram begins first and ends sooner than the levocardiogram, and consequently the T wave is inverted. When the left ventricle was warmed, the levocardiogram became shorter, and the T wave became upright, whereas if the right ventricle was warmed, the dextrocardiogram was shortened and the T wave became deeply inverted. The opposite effects were produced by cooling. Changes in the amplitude and the direction of the chief initial ventricular deflection were produced and explained in this same manner. They observed:

When the anterior surface of the heart was cooled by a thermal chamber covering portions of both right and left ventricles, oppositely directed T waves appeared as follows: *a*, a prolonged, inverted T wave appeared in lead I, indicating in this lead the influence of a prolonged levocardiogram which could have been derived only from the cooled anterior surface of the left ventricle; *b*, in lead III the T wave was upright and prolonged, indicating the influence in this lead of a prolonged dextrocardiogram which could have been derived only from the anterior surface of the right ventricle. Lead I therefore must have recorded preponderantly from the anterior surface of the left ventricle. The results obtained by warming the anterior surface also showed oppositely directed T waves in leads I and III. In

this case, however, T_1 was upright, indicating curtailment of the anterior dextrocardiogram. This substantiates the hypothesis that the anterior levocardiogram is recorded in lead I, while the anterior dextrocardiogram is recorded in lead III.

When the posterior surface of the heart was warmed, the T waves became inverted in lead I and upright in lead III, whereas after cooling the T wave became upright in lead I and inverted in lead III.

With respect to ventricular premature beats it was found that stimulation of the major portion of the left ventricle resulted in beats showing initial downward deflections in the three leads, while stimulation of the major portion of the right ventricle resulted in beats showing initial upward deflections in the three leads. Premature beats arising from the anterior septum were found to be comparable with ventricular complexes at present interpreted as having right axis deviation (initial deflection down in lead I and up in lead III), while the opposite is true of those arising from the posterior septum.

Hoff and Nahum and their associates indulge in little speculation with regard to how far their results might be used in explaining some of the electrocardiograms obtained on patients. Certainly their methods, especially the use of heat and cold, are not comparable to what might occur in a human being. Also, the levocardiograms and dextrocardiograms they obtained do not resemble in their initial portions (duration and form of QRS) the corresponding portions of true levocardiograms and dextrocardiograms. However, this difference may not vitiate all their conclusions, but any conclusions regarding the representation of various portions of the heart in leads I and III in dogs might not prove to be true for human beings, because the same regions of the heart are not in contact with good conductors.

White, Leach and Foote [18] have called attention to errors in existing methods of measurement of the PR (or PQ) interval and QRS duration in electrocardiograms. The authors point out that it is common practice to accept the longest intervals for PR and QRS as the correct ones in any given record and that the PR interval is usually measured in lead II. However, in occasional records the initial deflections of QRS in leads I and III are of equal amplitude but oppositely directed, thus producing an isoelectric phase in lead II. Thus, in measuring from the beginning of P to R in lead II, a portion of the QRS complex would be added which might be sufficient to make the apparent duration of PR abnormally long. This, in turn, might lead to a false interpretation of serious import, which was exactly the circumstance that first brought the matter

18. White, P. D.; Leach, C. E., and Foote, S. A.: Errors in Measurement of P-R (P-Q) Interval and QRS Duration in the Electrocardiogram, Am. Heart J. **22**:321, 1941.

to the authors' attention. A simple method of avoiding this error is presented, namely, subtracting the figure for the widest QRS wave from that for the longest PS duration (that is, from the beginning of P to the end of S).

It is now well known that a number of factors in addition to heart disease per se may cause lowering or inversion of the T waves of the electrocardiogram. Two recent papers [19] have emphasized the importance of the position of the heart in the thorax as a cause of significant lowering or inversion of the T waves in leads II and III. Most commonly the abnormal appearance of the T waves is observed when the record is obtained while a subject or patient is seated. On changing to the recumbent position, the T wave abnormalities disappear. Evidence is given to support the contention that the T wave changes are not due to anoxemia of the myocardium. The important practical conclusion is evident, namely, that it is often necessary to obtain an electrocardiogram when the patient is recumbent in order properly to evaluate lowering or inversion of the T waves in leads II and III.

Low voltage of the QRS complexes of an electrocardiogram in all of the limb leads has long been considered to be a significant finding. Because most of the electrocardiographic studies have been carried out on patients, in whom low voltage of the QRS complexes is not infrequently observed, this sign was commonly regarded as of pathologic significance. However, as electrocardiograms came to be taken on normal subjects in larger numbers, it was often found that the voltage of QRS in the limb leads was "abnormally" low, and this fact has recently been emphasized by Leach and associates.[20] They analyzed 300 cases in which there was low voltage of the QRS complexes (in one-third in the limb leads alone, in one-third in lead CF_4 alone and in one-third in all four leads) and found that many factors in addition to heart disease were responsible for the low voltage. Their study indicated that the solitary finding of low voltage of the QRS in any or all of the four leads studied is of little or no diagnostic value regarding the presence of heart disease or any other disorder. Bellet and Kershbaum [21] have found that one chest lead alone may yield curves of low voltage. They believe

19. (*a*) Scherf, D., and Weissberg, J.: The Alterations of the T-Waves Caused by a Change of Posture, Am. J. M. Sc. **201**:693, 1941. (*b*) White, P. D.; Chamberlain, F. L., and Graybiel, A.: Inversion of the T Waves in Lead II Caused by a Variation in Position of the Heart, Brit. Heart J. **3**:233, 1941.

20. Leach, C. E.; Reed, W. C., and White, P. D.: Low Voltage of the QRS Waves in the Electrocardiogram with Especial Reference to Lead IV, Am. Heart J. **21**:551, 1941.

21. Bellet, S., and Kershbaum, A.: The Significance of Low Voltage of the QRS Complex in Precordial Leads, Am. Heart J. **22**:195, 1941.

reliance should not be placed on a single precordial lead for a diagnosis of low voltage and that in addition to leads CF_3, CF_4 and CF_5, leads CB and CR should be taken. Using this criterion, they found that all of 20 patients who had low voltage both in the precordial and in the limb leads showed evidence of myocardial damage.

Weinberg and Katz [22] have called attention to an electrocardiographic pattern following cardiac infarction in which the T waves are simultaneously inverted in leads I, II and III. This pattern was found in about 16 per cent of their cases of a condition proved beyond reasonable doubt to be acute myocardial infarction. In some instances this pattern appeared at the onset, while in others it occurred at some later stage. It may occur as a transitory phenomenon or may remain for some time. The various possible mechanisms responsible for this pattern are discussed.

Kaplan and Katz [23] have described the characteristic electrocardiographic patterns in left ventricular strain with and without axis deviation. Mortensen [24] has contributed an interesting article on bundle branch block with particular reference to the changes observed in the chest leads. Other interesting articles include Bachmann's [25] report on the significance of splitting of the P waves, Knies's [26] report on the electrocardiogram in induced fever, Larsen and Skulason's [27] studies on the normal electrocardiogram and Levine and Beeson's [28] and Wolferth and Wood's [29] reports on short PR and wide QRS anomaly.

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22. Weinberg, H. B., and Katz, L. N.: A Common Electrocardiographic Variant Following Acute Myocardial Infarction, Am. Heart J. **21**:699, 1941.

23. Kaplan, L. G., and Katz, L. N.: The Characteristic Electrocardiograms in Left Ventricular Strain With and Without Axis Deviation, Am. J. M. Sc. **201**:676, 1941.

24. Mortensen, V.: Pathogenesis of Bundle Branch Block and Other Preponderance Curves, Acta med. Scandinav. **104**:267, 1941.

25. Bachmann, G.: The Significance of Splitting of the P-Wave in the Electrocardiogram, Ann. Int. Med. **14**:1702, 1941.

26. Knies, P. T.: The Electrocardiogram in Induced Fever, Am. Heart J. **22**:804, 1941.

27. (*a*) Larsen, K., and Skulason, T.: The Normal Electrocardiogram: I. Analysis of the Extremity Derivations from One Hundred Normal Persons Whose Ages Ranged from Thirty to Fifty Years, Am. Heart J. **22**:625, 1941. (*b*) Skulason, T., and Larsen, K.: The Normal Electrocardiogram: II. Analysis of Precordial Derivations *d* and *s* from One Hundred Normal Persons Whose Ages Ranged from Thirty to Fifty Years, ibid. **22**:645, 1941.

28. Levine, S. A., and Beeson, P. B.: The Wolff-Parkinson-White Syndrome, with Paroxysms of Ventricular Tachycardia, Am. Heart J. **22**:401, 1941.

29. Wolferth, C. C., and Wood, F. C.: Further Observations on the Mechanism of the Production of a Short P-R Interval in Association with Prolongation of the QRS Complex, Am. Heart J. **22**:450, 1941.

CARDIAC ARRHYTHMIAS

Ventricular Fibrillation.—Wiggers and his associates [30] have reported their further observations on ventricular fibrillation in dogs. They measured the fibrillation thresholds in normal dogs' hearts and during brief coronary occlusion. From this study they describe the probable mechanism which initiates spontaneous ventricular fibrillation following coronary occlusion. Acute ischemia

> . . . gives rise to many ectopic foci which release stimuli which are subthreshold as far as induction of fibrillation in the normal myocardiogram is concerned and it increases irritability sufficiently so that these stimuli become effective when they fall during the vulnerable phase.

Stokes-Adams Attacks.—Parkinson, Papp and Evans [31] have discussed the Stokes-Adams attack after a study of cases (8 of their own and 56 collected from the literature) in which an electrocardiogram was recorded during the period of unconsciousness. They would limit the meaning of the term and define it as follows:

> Stokes-Adams disease is a name applicable to patients with heart block who suffer from recurrent attacks of loss of consciousness due to ventricular standstill, ventricular tachycardia, ventricular fibrillation, or a combination of these.
>
> During a Stokes-Adams attack from ventricular standstill the auricle continues to beat, whereas in other cardiac syncopes as a rule there is total cardiac standstill.
>
> The term cardiac syncope may be reserved for attacks in patients without heart block due to total cardiac standstill from neurogenic or myocardial causes.

The authors point out that although it is widely believed that ventricular standstill is the only common disturbance of mechanism which determines loss of consciousness, there are other disturbances of rhythm which may be responsible for the cerebral attack. The following classification is given:

Group I. Ventricular standstill alone (33 of 64 cases). Although this is sometimes consecutive to an increase in ventricular rate, it is unlikely that exercise or emotion is more than a rare precipitating factor; the increase in auricular rate is probably spontaneous and originates in the auricle or the node itself. During a short ventricular standstill (below 20 seconds) the auricle beats regularly, whereas in a long ventricular standstill (above 20 seconds), as when it is preceded by high

30. (*a*) Wiggers, C. J.: The Ineffectiveness of Vagal Stimulation on Ventricular Fibrillation in Dogs, Am. J. Physiol. **133**:634, 1941. (*b*) Moe, G. K.; Harris, A. S., and Wiggers, C. J.: Analysis of the Initiation of the Fibrillation by Electrocardiographic Studies, ibid. **134**:473, 1941. (*c*) Wegria, R.; Moe, G. K., and Wiggers, C. J.: Comparison of Vulnerable Periods and Fibrillation Thresholds of Normal and Idioventricular Beats, ibid. **133**:651, 1941.

31. Parkinson, J.; Papp, C., and Evans, W.: The Electrocardiogram of the Stokes-Adams Attack, Brit. Heart J. **3**:171, 1941.

ventricular tachycardia and fibrillation, the auricle may slow, arrhythmia may develop or the auricle may stop. The Stokes-Adams attack due to ventricular standstill and that due to high ventricular tachycardia or ventricular fibrillation can be distinguished only by electrocardiogram. A late onset of consciousness or loss of consciousness of more than three minutes' duration is rarely due to ventricular standstill. The prognosis for patients showing ventricular standstill alone is much better than that for those showing high or low ventricular tachycardia and fibrillation.

Group II. Ventricular tachycardia followed by ventricular standstill.

(*a*) Low ventricular tachycardia (rate below 160) followed by ventricular standstill (4 cases). Low ventricular tachycardia does not produce unconsciousness, but it provokes the subsequent ventricular standstill which, of course, does cause unconsciousness.

(*b*) High ventricular tachycardia (rate between 200 and 500), usually also with ventricular fibrillation, followed by ventricular standstill (14 cases). The high ventricular tachycardia and fibrillation produce unconsciousness which may be prolonged by the subsequent standstill.

Group III. High ventricular tachycardia or ventricular fibrillation or both without ventricular standstill (13 cases). The prognosis both of the immediate attack and of survival is poor for patients in groups II and III.

Group IV. Extreme bradycardia with complete heart block. This is a small and unimportant group.

Auricular Fibrillation.—Modell, Gold and Rothendler [32] have shown that in the average patient with auricular fibrillation the increase in rate during exercise is due chiefly to decrease in vagal tone. Some confirmation of this fact was found in the observation that the increase in heart rate following atropinization was similar to the increase in rate after severe exercise. If patients with auricular fibrillation are given relatively large doses of digitalis ("extravagal" digitalization), the exaggerated acceleration of the ventricles caused by exercise can usually be prevented. They conclude that the small increase in rate following administration of large amounts of digitalis is due to the direct action of this drug on auriculoventricular conduction.

Hubbard's Syndrome.—Hubbard [33] has described a newly observed clinical syndrome, the course of which is circulatory failure resulting from paroxysmal tachycardia in infants less than 12 months of age. The incidence is unknown, but it is of interest that the author observed

32. Modell, W.; Gold, H., and Rothendler, H. H.: Use of Digitalis to Prevent Exaggerated Acceleration of the Heart, J. A. M. A. **116**:2241 (May 17) 1941.

33. Hubbard, J. P.: Paroxysmal Tachycardia and Its Treatment in Young Infants, Am. J. Dis. Child. **61**:687 (April) 1941.

6 of his 9 cases within a year, yet was able to collect only 19 cases from the medical literature. The diagnosis may be made clinically, but because of the difficulty in counting the pulse or even the heart rate accurately in young infants, electrocardiograms should always be obtained. The signs and symptoms are characteristic and include vomiting, which may be severe; dyspnea, with a respiratory rate as high as 160 per minute; fever; leukocytosis, and marked congestive phenomena, including cyanosis, cardiac enlargement, pulmonary congestion, engorgement of the liver and edema of dependent parts. The prognosis is unfavorable unless digitalis is promptly given. The recommended initial dose is 0.05-0.1 Gm. of digifoline intramuscularly, and this should be repeated at intervals (once or twice a day) until the desired effect is obtained. After digitalization has been accomplished, the heart rate and rhythm return to normal, and clinical improvement follows with dramatic abruptness. This condition has as a rule been wrongly diagnosed, for example, as congenital idiopathic hypertrophy, pyloric stenosis and pneumonia. The prognosis is apparently good, and there is little tendency for the arrhythmia to recur.

Potassium.—Despite the extensive knowledge of potassium metabolism and the part it plays in heart muscle contraction, there is some doubt and confusion with reference to the therapeutic use of potassium salts in cardiac arrhythmias. For many years the use of potassium was recommended for abolishing or preventing premature beats and paroxysmal tachycardia, and there is no doubt that this was attended with some success. On the other hand, it has also been pointed out by several observers that certain types of cardiac arrhythmia and alterations in the electrocardiogram result from the administration of potassium salts.

A partial explanation of these apparently conflicting results has been offered by Castleden,[34] and it would appear that in some patients, at least, with abnormally low serum potassium levels cardiac arrhythmias and electrocardiographic abnormalities can be abolished by administering potassium salts, whereas in patients with normal serum potassium levels who are given potassium salts cardiac irregularities and electrocardiographic abnormalities may develop.

CONGENITAL HEART DISEASE

Bedford, Papp and Parkinson[35] have reported at length their observations on atrial septal defect. They point out that this is one of the commonest congenital malformations and should be differentiated

34. Castleden, L. I. M.: The Effect of Potassium Salts on Cardiac Irregularities, Brit. M. J. **1**:7, 1941.

35. Bedford, D. E.; Papp, C., and Parkinson, J.: Atrial Septal Defect, Brit. Heart J. **3**:37, 1941.

from patent foramen ovale, which is simply an anatomic variation of a normal condition. The diagnosis of atrial septal defect can often be made clinically. Although this defect itself produces no murmurs, the accompanying dilatation of the right ventricle and conus and relative stenosis of the less distensible pulmonary ring account for the loud systolic murmur heard over the pulmonary area in three fifths of the cases. Accentuation of the pulmonary second sound is likewise a common finding, and an accompanying thrill is sometimes felt and a pulmonary diastolic murmur sometimes heard. The roentgen features are characteristic and include general enlargement of the heart, bulging of the pulmonary stem and conus and a dense shadow in the right hilus, with excessive pulsation. The electrocardiogram is often helpful in diagnosis, particularly the presence of right axis deviation. The association of mitral stenosis and atrial septal defect is stressed.

RHEUMATIC HEART DISEASE

Etiology.—Mote and Jones [36] have reported their extensive observations on the antibody responses to hemolytic streptococci in patients with primary or recurrent rheumatic fever. The antibody response was also studied in healthy persons and in patients with scarlet fever and with acute streptococcic pharyngitis. It was found that the rheumatic and the nonrheumatic patients have similar antibody responses to acute infection with hemolytic streptococci. Also, severe rheumatic infection may develop in patients without clinical or serologic evidence of infection with streptococci, or, on the other hand, streptococcic infection may occur in a rheumatic subject without precipitating active rheumatic fever. Mote and Jones's contribution is important but still leaves unexplained the exact role played by streptococci in the causation of rheumatic fever.

Kuttner and Krumwiede [37] have described in some detail the effects of three outbreaks of streptococcic infection of the upper respiratory

36. (*a*) Mote, J. R., and Jones, T. D.: Studies of Hemolytic Streptococcal Antibodies in Control Groups, Rheumatic Fever, and Rheumatoid Arthritis: I. The Incidence of Antistreptolysin 'O', Antifibrinolysin, and Hemolytic Streptococcal Precipitating Antibodies in the Sera of Urban Control Groups, J. Immunol. **41**:35, 1941; (*b*) Studies of Hemolytic Streptococcal Antibodies in Control Groups, Rheumatic Fever, and Rheumatoid Arthritis: II. The Frequency of Antistreptolysin 'O', Antifibrinolysin, and Precipitating-Antibody Responses in Scarlet Fever, Hemolytic Streptococcal Infections, and Rheumatic Fever, ibid. **41**:61, 1941; (*c*) Studies of Hemolytic Streptococcal Antibodies in Control Groups, Rheumatic Fever, and Rheumatoid Arthritis: III. The Magnitude of Antistreptolysin 'O', Antifibrinolysin, and Precipitating-Antibody Responses; the Persistence of the Antibodies, and Variations in Antistreptolysin 'O' Curves in Scarlet Fever, Hemolytic Streptococcal Infections, and Rheumatic Fever, ibid. **41**:87, 1941.

37. Kuttner, A. G., and Krumwiede, E.: Observations on the Effect of Streptococcal Upper Respiratory Infections on Rheumatic Children: A Three-Year Study, J. Clin. Investigation **20**:273, 1941.

tract in a colony of rheumatic children. The incidence of rheumatic recurrences was found to vary greatly, but a comparison of the epidemic strains of streptococci and of the clinical features of the infections failed to reveal any significant differences to account for this. The authors conclude that the vulnerability of a rheumatic subject to the effects of streptococcic infection of the upper respiratory tract is variable and depends on factors not yet understood.

Reyersbach, Lenert and Kuttner [38] studied an outbreak of influenza due to influenza virus B in a group of rheumatic children. No rheumatic recurrences were precipitated, and no evidence was obtained to suggest that the virulence of a group A beta hemolytic Streptococcus of proved pathogenicity was increased by this strain of influenza virus.

Glazebrook and Thomson [39] have briefly reported 11 instances of rheumatic fever in which the first evidence of rheumatic arthritis was in a traumatized joint. Their data do not prove that trauma was the sole, or even the chief, precipitating factor in the rheumatic infection, but there is little doubt that the trauma determined the initial location of joint disease.

Rheumatic Pneumonia.—Epstein and Greenspan [40] have reported their observations on the pulmonary changes in 45 cases of acute fatal rheumatic fever. They found characteristic pulmonary changes, including alveolitis, marked congestion, edema, engorgement and the formation of hyaline membranes but do not consider these changes specific; i. e., a specific rheumatic lung or rheumatic pneumonia cannot be considered to exist.

The Pulse Rate in Acute Rheumatism.—Glazebrook and Thomson [41] observed the pulse rate in 100 consecutive cases of acute rheumatism in boys and youths aged 15 to 20 years. They found that slowing of the pulse rate is a common feature in the initial stages of the first attack of rheumatic infection but that all patients showed tachycardia in the later stages. They divided the 100 cases into three groups. In the 38 cases in the first group the pulse rate was commensurate with the body temperature. There was some increase in pulse rate in the second group of 32 cases, but this increase was not commensurate with the temper-

38. Reyersbach, G.; Lenert, T. F., and Kuttner, A. G.: An Epidemic of Influenza B Occurring in a Group of Rheumatic Children Concurrent with an Outbreak of Streptococcal Pharyngitis: Clinical and Epidemiological Observations, J. Clin. Investigation **20**:289, 1941.

39. Glazebrook, A. J., and Thomson, S.: Acute Rheumatism and Trauma, Edinburgh M. J. **48**:674, 1941.

40. Epstein, E. Z., and Greenspan, E. B.: Rheumatic Pneumonia, Arch. Int. Med. **68**:1074 (Dec.) 1941.

41. Glazebrook, A. J., and Thomson, S.: The Pulse Rate in Acute Juvenile Rheumatism, Edinburgh M. J. **48**:619, 1941.

ature. Bradycardia occurred at an early stage of the illness in the remaining 30 cases which composed the third group and was usually a transient phenomenon. Bradycardia was sometimes associated with marked sinus arrhythmia and prolongation of the PR interval, all of which may have been due to vagal overstimulation. It was found that an abnormally slow pulse rate in the early stages of the rheumatic infection is of grave prognostic significance insofar as permanent cardiac damage is concerned.

Electrocardiographic Changes.—Orgain, Martin and Anderson [42] have reviewed previous studies on the electrocardiographic alterations in rheumatic fever in children and reported their own observations on 70 patients. Abnormalities in single or serial tracings were found in 70 per cent of the 70 patients. They found that the electrocardiograms were abnormal in all of the 22 patients who had the most extensive myocardial damage.

Complications.—Harris and Levine [43] studied 72 cases of mitral stenosis in which cerebral embolism occurred. There were 24 "immediate fatalities," and in the 15 cases in which the patients died subsequently the average period of survival was a little over one year. Auricular fibrillation was present in 55 cases and regular rhythm in the remaining 17. In 5 instances cerebral embolism occurred a few hours or a day or two after a change from auricular fibrillation to normal rhythm. The difficulties of analyzing the factors responsible for the formation and dislodgment of auricular thrombi are emphasized. Despite the general assumption that auricular fibrillation increases the likelihood of thrombosis and embolism, Harris and Levine on the basis of their studies could not prove this assumption.

Wolff and Levine [44] found that about 10 per cent (50 of 521) of their series of patients with rheumatic heart disease had had hemoptysis. Mitral stenosis was present in every patient save 1 in which the hemorrhage was caused by a pulmonary abscess. The hemorrhage was accounted for by pulmonary infarction in almost half of the patients, but if the heart is not enlarged it can be excluded as a cause. Hemorrhage may be caused by active rheumatic infection or by mitral stenosis alone. The three most commonly associated symptoms were palpitation, pain in the chest and dyspnea. Insofar as prognosis is concerned hemoptysis is a grave sign.

42. Orgain, E. S.; Martin, J. M., and Anderson, H. I. G.: Electrocardiographic Alterations in Rheumatic Fever in Children, Am. J. Dis. Child. **62**:26 (July) 1941.

43. Harris, A. W., and Levine, S. A.: Cerebral Embolism in Mitral Stenosis, Ann. Int. Med. **15**:637, 1941.

44. Wolff, L., and Levine, H. B.: Hemoptysis in Rheumatic Heart Disease, Am. Heart J. **21**:163, 1941.

Treatment.—Early studies on the use of sulfanilamide and some of its derivatives in the treatment of rheumatic heart disease, which have been previously reviewed,[45] led to the conclusion that during the active stage of the disease toxic rather than beneficial results were obtained, but that the long-continued prophylactic use of sulfanilamide prevented hemolytic streptococcic infection and recurrences of rheumatic fever. A further report by Thomas, France and Reichsman [46] has confirmed the earlier impression regarding the prophylactic use of sulfanilamide. The results of their carefully controlled studies are striking. A major attack of acute rheumatic fever or an acute infection caused by beta hemolytic streptococci did not develop in any of the 55 patients (79 person-seasons) who received sulfanilamide (usually 0.6 Gm. twice a day from November through June). Fifteen major attacks of acute rheumatic fever occurred in 67 patients (150 person-seasons) with a similar history who did not receive the drug. Furthermore, 4 deaths occurred in the control (nontreated) group, 2 as a result of subacute bacterial endocarditis, whereas there were no deaths among patients in the treated group. No serious toxic effects of sulfanilamide were observed. Thus, the studies of Thomas and associates, as well as those of others, point the way toward a better treatment of patients susceptible to rheumatic fever. These studies also add further proof of the close relation between infections caused by beta hemolytic streptococci and rheumatic infection.

SUBACUTE BACTERIAL ENDOCARDITIS

Although the results of chemotherapy of subacute bacterial endocarditis [47] have been disappointing, it is better than anything previously

45. (*a*) Graybiel, A.: Diseases of the Heart: A Review of Significant Contributions Made During 1938, Arch. Int. Med. **63**:980 (May) 1939. (*b*) Graybiel and White.[14]

46. Thomas, C. B.; France, R., and Reichsman, F.: The Prophylactic Use of Sulfanilamide, J. A. M. A. **116**:551 (Feb. 15) 1941.

47. (*a*) Leach, C. E.; Faulkner, J. M.; Duncan, C. N.; McGinn, S.; Porter, R. R., and White, P. D.: Chemotherapy and Heparin in Subacute Bacterial Endocarditis, J. A. M. A. **117**:1345 (Oct. 18) 1941. (*b*) Druckman, J. S.: A Case of Subacute Bacterial Endocarditis, ibid. **117**:101 (July 12) 1941. (*c*) Heyer, H. E., and Hick, F. K.: Experiences in the Treatment of Subacute Bacterial Endocarditis with Sulfanilamide, Sulfapyridine and Sulfathiazole: A Review of Previously Reported Cured Cases with the Report of Fifteen Treated Cases Including One Cure and One Aborted Case, Ann. Int. Med. **15**:291, 1941. (*d*) Kinsella, R. A.: Chemotherapy of Bacterial Endocarditis Caused by a Hitherto Undescribed Gram Negative Coccus, ibid. **15**:756, 1941. (*e*) Weber, F. P.: Recovery from the Infection of Subacute Bacterial Endocarditis Without Sulphonamides, Lancet **1**:630, 1941. (*f*) Solomon, H. A.: Subacute Bacteriai Endocarditis: Treatment with Sulfapyridine and Intravenous Injections of Typhopara-

(Footnote continued on next page)

tried. Probably cure is obtained in 1 case in 20 today, whereas spontaneous cures in the past were exceedingly rare indeed. Heparin, hyperpyrexia and fever induced by injection of typhoid vaccine have been used in conjunction with sulfanilamide and some of its derivatives, but enthusiasm for any combination treatment is waning. Sulfapyridine, (2-[paraaminobenzenesulfonamido]-pyridine), of the various compounds, seems to be the best, and it is advisable to keep the level of the drug in the blood high (10 mg. per hundred cubic centimeters) for at least a month, then to continue administering a reduced dose for two or three months longer. If the results are not promising, a change to sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) should be made.

The most promising results are being obtained in patients with patent ductus arteriosus complicated by subacute bacterial endoarteritis.[48] Obliteration of the ductus by surgical means together with chemotherapy has now resulted in a number of cures.

OTHER INFECTIONS

Scarlet Fever.—Wesselhoeft[49] has had the unusual experience of studying over 12,000 cases of scarlet fever and must be regarded as an authority on the cardiovascular disorders or complications in this disease. He points out that the endocarditis which may develop in the course of scarlet fever is the result of infection of the blood stream and constitutes a true bacterial endocarditis. He does not believe that scarlet fever causes valvular endocarditis comparable to that seen in rheumatic infection; a valvular defect which appears late after scarlet fever should be considered to be of rheumatic origin. Severe myocarditis, such as may occur in the course of diphtheria, is rarely observed in scarlet fever, and when it occurs, there is a strong possibility that diphtheria is present as a complication. Wesselhoeft states that of 9 cases of severe myocarditis among 12,820 cases of scarlet fever, cultures positive for the diphtheria bacillus were obtained in 6. He discusses in some detail

typhoid Vaccine, New York State J. Med. **41**:45, 1941. (*g*) Southworth, H.: Subacute Staphylococcus Endocarditis and Staphylococcus Bacteremia Without Endocarditis with a Report of the Favorable Effect of Sulfanilamide and Sulfathiazole in Two Cases, Ann. Int. Med. **14**:1180, 1941. (*h*) Sevitt, S.: Treatment of Bacterial Endocarditis with Heparin and Sulfapyridine, Lancet **1**:444, 1941. (*i*) McLean, J.; Meyer, B. B. M., and Griffith, M. F.: Heparin in Subacute Bacterial Endocarditis, J. A. M. A. **117**:1870 (Nov. 29) 1941. (*j*) Cockayne, E. A., and Wilton, T. N. P.: Acute Bacterial Endocarditis, Lancet **2**:728, 1941.

48. Bourne, G.; Keele, K. D.; Tubbs, O. S., and Swain, R. H. A.: Ligation and Chemotherapy for Infection of Patent Ductus Arteriosus, Lancet **2**:444, 1941.

49. Wesselhoeft, C.: Cardiovascular Disorders in Scarlet Fever, New England J. Med. **224**:22, 1941.

the so-called "scarlet fever heart," diagnosis of which is usually dependent on the development of murmurs which are so variable in time and character as not to be distinctive. Tachycardia or bradycardia may develop, but there is rarely any cardiac enlargement, and there is no precordial pain or discomfort. All these signs are ephemeral and disappear in the course of one to three weeks.

Wesselhoeft agrees that minor electrocardiographic abnormalities may appear, but states that they are not peculiar to scarlet fever and do not constitute proof of myocarditis. Roelsen,[50] however, believes that the more significant and persistent electrocardiographic changes are probably due to pathologic changes in the myocardium, but that the slight and transient changes are likely due to myocardial toxemia.

With respect to treatment Wesselhoeft believes that in the toxic myocarditis accompanying scarlet fever specific drugs are of no value, but that if endocarditis or pericarditis of bacterial origin supervene, sulfanilamide should be given.

Tuberculosis.—Hannesson [51] has written an excellent article on tuberculosis of the pericardium and the heart. He states that although the myocardium and the endocardium are rarely involved in tuberculosis, involvement of the pericardium is not as rare as is generally supposed and is the most serious tuberculous infection of the serous membranes. He believes that most instances of tuberculous pericarditis are due to an extension of the infection through lymph channels from a mediastinal focus, but that infection may occur in a neighboring structure. Hannesson divides the pathologic progress in a typical case into three stages. An acute fibrinous stage passes fairly rapidly into the stage of pericardial thickening and effusion. The third stage is that in which the effusion has largely disappeared and the pericardium is greatly thickened. This may be so extensive as to give rise to typical Pick's disease.

The author points out that tuberculous pericarditis is protean in its clinical manifestations and that the clinical features depend on the nature of the onset, the type of pathologic changes, the duration of the disease and other factors. The symptomatology and clinical features are described in detail. He summarizes the important findings necessary to make a diagnosis of tuberculous pericarditis as follows:

> The signs and symptoms of an infection should be present; there should be localizing signs over the pericardium such as pericardial friction rub, signs of pericardial effusion and thickening of the pericardium, and the signs of adhesions. There should be signs of circulatory failure of the "inflow stasis" type; there should be signs of extension of the process to other serous sacs or a disseminated

50. Roelsen, E.: Electrocardiographic Studies in Scarlet Fever, Acta med. Scandinav. **106**:1, 1941.

51. Hannesson, H.: Tuberculosis of the Pericardium and Heart, Tubercle **22**: 79, 1941.

tuberculosis; a normal or small heart should be demonstrated after the production of a pneumopericardium; a careful x-ray study should be made.

A clinical diagnosis can be made on the results of a careful physical and radiological examination.

An exact diagnosis can only be made by demonstration of tubercle bacilli in the pericardial fluid.

Hannesson points out that present methods of treatment of tuberculous pericarditis are unsatisfactory and that the prognosis is bad (83 per cent). It is of interest that he considers polyserositis in all probability to be tuberculous in origin and a condition associated with a high degree of immunity to the infection. He was unable to determine any exact relation between pulmonary tuberculosis and diseases of the heart.

ARTERIAL HYPERTENSION

Experimental Aspects.—Because of the importance of this subject, it seems worthwhile to review again the main developments and the present status of knowledge with regard to experimental hypertension and the resulting clinical implications. The current phase of this work began with the demonstration by Goldblatt that if one or both of the main renal arteries of a dog were partially occluded by a metal clamp, hypertension would result.

This was quickly confirmed by many other investigators and amplified to the extent that various methods were shown to be capable of producing lasting hypertension ranging from the benign to the malignant variety.

An immediate search was begun for the factors or substances responsible for the hypertension, and largely by the process of exclusion, it was soon shown that a humoral factor elaborated by the kidney was the probable cause. At this point it was recalled that Tigerstedt and Bergmann in 1898 obtained a pressor substance from renal tissue extract, which was called renin, and this seemed the most likely substance to investigate.

The characteristics of renin have been studied extensively, and it has been shown that a renin-like substance is liberated in increased amounts by the kidneys of dogs made hypertensive by one of the several available methods. However, attempts to demonstrate an increased amount of renin in the extracts of kidneys of hypertensive patients as compared with normal controls has not yet yielded convincing results.[52]

Page and his associates have shown that purified renin alone does not cause vasoconstriction when perfused in Ringer's solution through a rabbit's ear. It requires the addition of a substance found normally in plasma which has been given the name "renin-activator." The product

52. Landis, E. M.: Hypertension and the Pressor Activity of Heated Extracts of Human Kidneys, Am. J. M. Sc. **202**:14, 1941.

of the interaction between renin and renin-activator is a third substance, to which Page has given the name angiotonin.

Angiotonin exerts a powerful vasopressor action [53] but is distinguishable from most other pressor substances in that it does not appreciably diminish cutaneous blood flow. Much more important is the fact that animals which have received repeated injections of renin fail to respond with a rise in arterial pressure (tachyphylaxis), which appears to be due to the release of a substance which antagonizes renin or its reaction product angiotonin. Studies along this line [54] have definitely shown that this substance which opposes the action of angiotonin is elaborated in the kidneys and is capable of lowering the blood pressure. Grollman and his associates, Page and his co-workers and the Argentinian investigators have obtained this antipressor substance, using different methods. All groups of workers have had some success in lowering the blood pressure in animals made hypertensive and in patients with essential or malignant hypertension. Page and his associates have now administered this extract to 280 hypertensive dogs, 13 patients with malignant hypertension and 6 patients with essential hypertension. They found that the extract prepared from 400 to 900 Gm. of fresh pork kidney is usually required to reduce the blood pressure of a dog weighing 12 Kg. from 200 to 130 mm. of mercury. The extracts were usually given in moderate doses daily. Arterial pressure began to fall in two to four days, reaching nearly normal levels in five to eight days. Discontinuing the extract did not lead to an immediate rise in blood pressure; usually several days elapsed before there began a gradual rise in pressure to the original hypertensive level. Good results were also obtained in dogs

53. Page, I. H.: The Pressor Response of Normal and Hypertensive Dogs to Renin and Angiotonin, Am. J. Physiol. **134**:789, 1941.

54. (*a*) Corcoran, A. C.; Kohlstaedt, K. G., and Page, I. H.: Changes of Arterial Blood Pressure and Renal Hemodynamics by Injection of Angiotonin in Human Beings, Proc. Soc. Exper. Biol. & Med. **46**:244, 1941. (*b*) Bradley, S. E., and Parker, B.: The Hemodynamic Effects of Angiotonin in Normal Man, J. Clin. Investigation **20**:715, 1941. (*c*) Wilkins, R. W., and Duncan, C. N.: The Nature of the Arterial Hypertension Produced in Normal Subjects by the Administration of Angiotonin, ibid. **20**:721, 1941. (*d*) Grollman, A.; Williams, J. R., Jr., and Harrison, T. R.: The Reduction of Elevated Blood Pressure by Administration of Renal Extracts, J. A. M. A. **115**:1169 (Oct. 5) 1940. (*e*) Jensen, H.; Corwin, W. C.; Tolksdorf, S.; Casey, J. J., and Bamman, F.: Reduction of Arterial Blood Pressure of Hypertensive Rats by Administration of Renal Extracts, J. Pharmacol. & Exper. Therap. **73**:38, 1941. (*f*) Page, I. H.; Helmer, O. M.; Kohlstaedt, K. G.; Kempf, G. F.; Gambill, W. D., and Taylor, R. D.: The Blood Pressure Reducing Property of Extracts of Kidneys in Hypertensive Patients and Animals, Ann. Int. Med. **15**:347, 1941. (*g*) Page, I. H.; Helmer, O. M.; Kohlstaedt, K. G.; Fouts, P. J., and Kempf, G. F.: Reduction of Arterial Blood Pressure of Hypertensive Patients and Animals with Extracts of Kidneys, J. Exper. Med. **73**:7, 1941.

made severely hypertensive and exhibiting the malignant syndrome. The blood urea nitrogen usually falls as the blood pressure drops, and there may be dramatic clinical improvement.

After one reads the 19 case histories reported by Page and associates the general impression is gained that the treatment of severe hypertension by means of renal extracts is still far from satisfactory. Systolic and diastolic blood pressures are lowered significantly in some cases, and associated with this there is considerable clinical improvement. However, severe reactions are often encountered, with symptoms resembling shock and followed by fever. These untoward side-effects prohibit this form of treatment in cases of mild essential hypertension in which the best results would be expected. There is, as yet, no sure proof that these extracts have more than a nonspecific effect, but with further purification this important point should be clarified. The many investigators in various centers working on this problem should be encouraged to continue. Their work represents a hopeful line of research in the pathogenesis and treatment of hypertension.

Bing and Zucker [55] have studied the pressor effect of several amino acids metabolized by the ischemic kidney. It is known that certain renal extracts transform amino acids into the corresponding amines, some of which have a pressor action. Normally, these amines are broken down into physiologically inert end-products, but under anaerobic conditions this is prevented and the amines are free to exert their pressor action. The authors put this to a practical test by injecting amino acids into the kidneys of experimental animals. With the renal circulation intact no significant pressor effects were noted, but when the circulation was restricted the arterial pressure rose. That altered amino acid metabolism may be responsible for renal hypertension is the interesting suggestion put forth.

Wilson and Byrom [56] have contributed important experimental observations which go a long way toward explaining the clinical and histologic manifestations which are common to the end stages of Bright's disease. They produced hypertension in rats by partial occlusion of one renal artery. After a time the clamped kidney was removed, but residual hypertension remained in two thirds of the animals. The degree of hypertension was found to be related to the extent of the lesions in the remain-

55. (*a*) Bing, R. J.: The Formation of Hydroxytyramine by Extracts of Renal Cortex and by Perfused Kidneys, Am. J. Physiol. **132**:497, 1941. (*b*) Bing, R. J., and Zucker, M. B.: The Formation of Pressor Amines in the Kidney, Proc. Soc. Exper. Biol. & Med. **46**:343, 1941; (*c*) Renal Hypertension Produced by Amino Acids, J. Exper. Med. **74**:235, 1941.

56. Wilson, C., and Byrom, F. B.: The Vicious Circle in Chronic Bright's Disease: Experimental Evidence from the Hypertensive Rat, Quart. J. Med. **10**: 65, 1941.

ing kidney, which resemble those occurring in cases of chronic hypertensive Bright's disease. They conclude that their findings support the concept of a vicious circle resulting from the effect of hypertension on the kidney whereby hypertension produces vascular lesions and these, by reducing the blood flow through the kidney, aggravate the hypertension, which in turn leads to sustained hypertension and progressive renal destruction.

CORONARY ARTERIOSCLEROTIC HEART DISEASE

Etiology.—From a long experience Hueper [57] has formulated a definite opinion regarding the etiology and the causative mechanism of arteriosclerosis and atheromatosis. His introduction is as follows:

> No agreement has been reached concerning the respective roles played in the production of these lesions, on the one hand by physiological senescing processes, possibly conditioned in their time of onset, in their rate of progress, and in their organic distribution by constitutional or hereditary factors, and on the other hand by pathological disturbances of endogenous or exogenous origin and of acquired nature. The situation existing in this respect is complicated by the fact that these vascular manifestations exhibit a remarkable diversity in their anatomical structure, as evidenced by the various names used, such as arteriosclerosis, atheromatosis, atherosclerosis, Monckeberg's media necrosis and calcification, etc., indicating that several fundamentally different causal factors may be reflected by these morphological varieties. The same conclusion is suggested by the observation that there occurs a considerable disparity in the organic distribution and in the time of appearance of these lesions in the different organs. None of the numerous theories so far advanced concerning the etiology of degenerative vascular disease supplies a satisfactory explanation of the multitude and variety of phenomena, or provides an acceptable common denominator of the primary causal dynamics operating in their production.

Hueper then discusses a number of endogenous and exogenous factors of a physical and chemical nature which have been considered etiologically significant in the development of vascular lesions. These are grouped under five headings, namely, (1) physiologic senescing processes, (2) physiologic and pathologic mechanical traumas, (3) infections and bacteriotoxic agents, (4) physiochemical disturbances of the blood of endocrine, vitaminic or nutritive origin and (5) agents affecting the vascular tonus and the circulation of the blood. He reaches the general conclusion that the fundamental causal mechanism of degenerative arterial disease is impaired nutrition and oxygenation of the vascular wall, resulting in endothelial damage, increased intimal permeability and the infiltration of plasma into the subintimal tissue followed by the proliferation of endothelial cells and the degeneration of the muscular and the elastic cells.

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57. Hueper, W. C.: The Etiology and the Causative Mechanism of Arteriosclerosis and Atheromatosis, Medicine **20**:397, 1941.

Hueper emphasizes that a rational therapeutic management of arteriosclerotic patients depends in part on the determination of the etiologic agent, which is admittedly difficult because of the great complexity of present day life. But, says Hueper, the outstanding therapeutic procedure, apparently capable of preventing the development of or arresting the progress of arteriosclerosis of varying causation, is represented by a maintenance of an adequate oxygen metabolism; thyroid and iodine preparations have proved so far to be the most suitable agents for attaining this end, particularly in cases in which an endogenous disturbance of the oxygen metabolism prevails.

The Precipitating Factors in Coronary Occlusion.—Paterson [58] has again emphasized the important role of intimal hemorrhage in producing coronary thrombosis. This hypothesis has received strong support from various investigators and most recently from Nelson.[59] He observed that hemorrhage from sinusoidal blood vessels which are found in relation to atheromatous plaques is not uncommon and that superficial intimal hemorrhage is a most important factor in the causation of coronary occlusion. Nelson is in agreement with Paterson that the factors determining the hemorrhage are probably weakening of the sinusoidal wall by toxic action and increase in blood pressure induced by exertion or emotion. Paterson [58] considers that increased capillary fragility due to vitamin C deficiency may also be a causative factor and that calcification of atherosclerotic plaques may be a protection against intimal hemorrhage and recommends an ample calcium intake.

Blumgart, Schlesinger and Zoll [60] in a study of the clinical and pathologic findings in a series of 350 cases observed multiple fresh coronary occlusions in 11. In 8 of the 11 cases multiple fresh thrombi had occluded the arteries, while in the remaining 3 the multiple occlusions were due to hemorrhages within atheromatous plaques and to ruptured atheromatous abscesses. In each instance the multiple occlusions occurred in the presence of shock which was due to conditions other than myocardial infarction in 8 of the 11 cases. They conclude that shock, no matter how produced, may lead in elderly patients to the development not only of single but of multiple fresh coronary artery occlusions and that measures to prevent the manifestations of shock should always be taken.

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58. Paterson, J. C.: Some Factors in Causation of Intimal Hemorrhages and in Precipitation of Coronary Thrombi, Canad. M. A. J. **44**:114, 1941.

59. Nelson, M. G.: Intimal Coronary Artery Hemorrhage as a Factor in the Causation of Coronary Occlusion, J. Path. & Bact. **53**:105, 1941.

60. Blumgart, H. L.; Schlesinger, M. J., and Zoll, P. M.: Multiple Fresh Coronary Occlusions in Patients with Antecedent Shock, Arch. Int. Med. **68**:181 (Aug.) 1941.

Clinical Aspects.—Walsh and his associates [61] found that disease of the gallbladder occurred almost twice as often in patients with coronary disease as in those with normal coronary arteries, probably primarily because of some common aging factor and not more intimate connection, whereas there was no significant association of peptic ulcer and coronary disease in general. Hochrein and Schleicher,[62] on the other hand, believe that there is a close relation between coronary insufficiency and peptic ulcer and cite clinical observations to this effect. Rosenbaum and Levine [63] have studied various clinical and electrocardiographic features of acute myocardial infarction and conclude that although the immediate outlook is difficult to predict and the ultimate course varies a great deal, a careful weighing of all the available information will materially aid in judging the prognosis. Bland and White [64] have obtained the after-history for the first ten years of 200 patients with coronary oclusion and acute myocardial infarction; of the entire series, 19 per cent died within the first four weeks and 31 per cent of the remainder survived the ten year period. Master, Dack and Jaffe [65] have summarized their studies which have been in part previously reviewed, based on the analysis of 1,700 proved attacks, especially on precipitating factors in coronary occlusion and myocardial infarction. Stroud and Wagner [66] have reported their findings in 49 cases of proved myocardial infarction in 13 of which the patients were without pain; they discuss various pain "equivalents" and emphasize the importance of recognizing painless infarction.

Induced Anoxemia in Patients with Coronary Arteriosclerotic Heart Disease.—Levy and his associates [67] have reported further on the

61. Walsh, B. J.; Bland, E. F.; Taquini, A. C., and White, P. D.: Association of Gallbladder Disease and of Peptic Ulcer with Coronary Disease: Postmortem Study, Am. Heart J. **21**:689, 1941.

62. Hochrein, M., and Schleicher, I.: Peptic Ulcer and Angina Pectoris, München. med. Wchnschr. **88**:328, 1941.

63. Rosenbaum, F. F., and Levine, S. A.: Prognostic Value of Various Clinical and Electrocardiographic Features of Acute Myocardial Infarction, Arch. Int. Med. **68**:912 (Nov.) 1941.

64. Bland, E. G., and White, P. D.: Coronary Thrombosis (with Myocardial Infarction) Ten Years Later, J. A. M. A. **117**:1171 (Oct. 4) 1941.

65. Master, A. M.; Dack, S., and Jaffe, H. L.: (*a*) Premonitory Symptoms of Acute Coronary Occlusion: Study of Two Hundred and Sixty Cases, Ann. Int. Med. **14**:1155, 1941; (*b*) Role of Effort, Work and Occupation on Onset and Subsequent Course of Coronary Artery Occlusion, M. Ann. District of Columbia **10**:79, 1941.

66. Stroud, W. D., and Wagner, J. A.: Silent or Atypical Coronary Occlusion, Ann. Int. Med. **15**:25, 1941.

67. Levy, R. L.; Williams, N. E.; Bruenn, H. C., and Carr, H. A.: The "Anoxemia" Test in the Diagnosis of Coronary Insufficiency, Am. Heart J. **21**:634, 1941.

"anoxemia test" in the diagnosis of coronary insufficiency. The test consists of having the patient breathe a mixture of 10 per cent oxygen and 90 per cent nitrogen for twenty minutes or until symptoms appear; electrocardiograms are taken before, during and after the induction of anoxemia. This test was performed on 115 normal persons and 147 patients with suspected or manifest cardiac disease. On the basis of this experience the response to the test was considered abnormal when any one (or more) of the following changes was observed:

1. The arithmetic sum of the RS-T deviations in all four leads (I, II, III and IVF) totals 3 mm. or more.

2. There is partial or complete reversal of the direction of T in Lead I, accompanied by an RS-T deviation of 1 mm., or more, in this lead.

3. There is complete reversal of the direction of T in Lead IVF, regardless of RS-T deviation.

4. There is partial reversal of the direction of T in Lead IVF, accompanied by an RS-T deviation of 1 mm., or more, in this lead.

Levy and co-workers state:

The test was positive in 18 per cent of 33 patients with suspected coronary sclerosis; in 31 per cent of twenty-two patients with coronary sclerosis but no history of anginal attacks; in 55 per cent of seventy-three patients with coronary sclerosis and a history of anginal attacks; and in only 5 per cent (one case) of nineteen patients with hypertension without symptoms or signs of coronary sclerosis. Patients whose control electrocardiogram was abnormal showed a higher percentage of positive tests than those with a normal control tracing. The highest incidence of positive tests was obtained in a group of forty-nine patients with anginal pain caused by coronary sclerosis and abnormal control electrocardiograms; in 69 per cent of these an abnormal response was obtained.

Pulmonary edema occurred during the test in 3 instances but was subsequently avoided by observing three rules, namely:

1. The test should never be performed in the presence of congestive heart failure.
2. It should not be performed within 4 months after cardiac infarction.
3. It should not be done on the same patient more than once in twenty-four hours.

Unpleasant effects occurred in 17 cases, including vasovagal attacks, convulsions, hyperventilation, dyspnea and mental confusion, but they did not prove serious.

The authors conclude that a positive test is a sign of functional insufficiency of the coronary circulation and that it may be usefully employed clinically. Williams and associates [68] used this test in evaluating the effects of certain xanthine drugs in cases of coronary insufficiency and concluded that in some cases the therapeutic response is favorable.

68. Williams, N. E.; Carr, H. A.; Bruenn, H. G., and Levy, R. L.: Further Observations on Effects of Certain Xanthine Compounds in Cases of Coronary Insufficiency, as Indicated by Response to Induced Anoxemia, Am. Heart J. **22**:252, 1941.

MISCELLANEOUS

Aneurysm of the Pulmonary Artery.—Boyd and McGavack [69] have presented the clinical picture of aneurysm of the pulmonary artery as a result of a study of 151 recorded instances of this disease. The chief etiologic and precipitating factors were congenital anomalies, pulmonary hypertension, atheromatosis and infection, of which syphilis appeared to have been present and active in over 30 per cent. The authors have divided the cases of pulmonary aneurysm into two main groups, namely, (1) those in which the trunk alone or in combination is involved and (2) those in which one or both branches are affected. They state that the former group is recognizable on the basis of signs and symptoms, whereas in the latter the condition gives rise to symptoms alone. They further state:

> Antemortem diagnosis is difficult in both clinical types, but can be established with a fair degree of accuracy in the first group if the following are simultaneously present: stasis in the lesser circulation, characterized by dyspnea, cyanosis, oppression of the chest, and bloody sputum; prominence of the left side of the chest in the region of the second and third costal cartilages; a pulsation, a thrill, and a loud superficial, sawing or rubbing systolic murmur, best heard at the second left intercostal space; a weak cardiac thrust with dulness not going beyond the midclavicular line; hypertrophy and dilatation of the right side of the heart; electrocardiographic evidence of right axis deviation; roentgenographic demonstration of lengthening and lateral projection of the pulmonary conus shadow in the anterior view, with a see-saw movement of the left border; indentation of the esophagus below the normal aortic impression in the right anterior oblique position; and encroachment upon the ventral and caudad aspects of the aortic window in the left anterior oblique visualization.
>
> The subjective symptoms are similar in the two groups. Cough occurs in 80 per cent of the cases, but is rarely an early manifestation. It depends upon pressure on the recurrent laryngeal nerve, in which event it is non-productive; upon bronchial irritation with at first a dry, and later a productive phase; or upon pulmonary thromboses when it is blood-streaked or frankly hemorrhagic.

The authors recognize that a number of conditions may simulate the clinical picture of aneurysm of the pulmonary artery and discuss the differential diagnosis. The chief lesions with which it may be confused are aortic aneurysm, patent ductus arteriosis, idiopathic dilatation of the pulmonary artery, interauricular septal defects and other congenital cardiac lesions.

We wish to point out that a clinical diagnosis of uncomplicated pulmonary aneurysm must be regarded with great skepticism, and therefore in 35 of the 151 cases (in which the condition was not confirmed by autopsy) the diagnosis is open to question.

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69. Boyd, L. J., and McGavack, T. H.: Aneurysm of the Trunk and Main Branches of the Pulmonary Artery: Analysis of One Hundred and Fifty-Two Cases, Mod. Concepts Cardiovasc. Dis. **10**:2, 1941.

Disseminated Lupus Erythematosus.—There are a number of disease syndromes, including disseminated lupus erythematosus, dermatomyositis and periarteritis nodosa, the causes of which are unknown but which have certain clinicopathologic features in common, including involvement of the cardiovascular system. The amount of attention they have received from cardiologists is probably greater than is deserved, as there is little evidence that the cardiac changes are more than incidental. Two recent reviews [70] have brought present knowledge up to date, without, however, resolving the problem. The nearest thing to a definite cardiac syndrome appears in those cases of disseminated lupus in which there is atypical verrucous endocarditis (Libman-Sacks syndrome). Despite the characteristic pathologic changes in these lesions, they are, with probable rare exceptions, too slight to yield definite clinical signs of heart disease and are rarely, if ever, the cause of congestive heart failure. Keil states:

> It seems probable that the area of distribution of these verrucae and the manner in which they are deposited contribute but little to the signs and symptoms in this disease. Most of the audible murmurs are, in all likelihood, attributable to extraneous factors, except in the relatively uncommon cases in which old valvular changes are encountered. The simultaneous occurrence of a pericardial rub makes the existence of gross endocardial involvement more probable as these two parts of the cardiac structure are often concurrently affected, but this rule has exceptions.

The diagnosis of disseminated lupus is usually made from the nature of the constitutional symptoms and the appearance of characteristic cutaneous lesions or signs of visceral disturbances. The diagnosis of Libman-Sacks syndrome may be suspected if signs of pericarditis and endocarditis appear but must be verified by postmortem examination. No adequate treatment is known, and the prognosis is uniformly bad.

Hiatus Esophagael Hernia.—Jones [71] has made a study of 128 patients with hiatus hernia, particularly from the standpoint of comparing the symptomatology in these patients with the symptomatology in patients suffering from heart disease. This group represented selected material only in that definite information regarding the size of the hernia was required and that only those patients were included whose presenting symptoms were referable to the hernia. The average age was 55. Concomitant diagnoses of heart disease (22) and biliary tract disease (22) were made for 44 patients. However, of the 22 patients with complicating

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70. (*a*) Keil, H.: Dermatomyositis and Systemic Lupus Erythematosus, Arch. Int. Med. **66**:110 (July) 1940. (*b*) Banks, B. M.: Is There a Common Denominator in Scleroderma, Dermatomyositis, Disseminated Lupus Erythematosus, the Libman-Sacks Syndrome and Polyarteritis Nodosa? New England J. Med. **225**: 433, 1941.

71. Jones, C. M.: Hiatus Esophageal Hernia, New England J. Med. **225**:963, 1941.

heart disease, Jones considered that only 11 had symptoms which might have contributed to the presenting symptomatology. Of the 128 patients, 91 had small hernias and 37 had large ones.

He found that substernal pain was experienced by over one third of the 91 patients with small hernias but occurred in only 5 of the 37 with large hernias. Shoulder pain, usually on the left, was noted by about one fourth of all the patients and radiation of pain into the arm by 12. Epigastric pain was noted by over 50 per cent of the patients. The records of 50 patients were sufficiently detailed to permit careful analysis of the pain. Twenty-five of the 50 patients complained of substernal pain, and 8 of these stated it was frequently, though not invariably, initiated by exercise, and 12 stated that emotional experiences frequently caused the pain to appear. As many as 15 of the 25 patients found that food, particularly a large meal, was responsible for initiating pain. Glyceryl trinitrate frequently afforded relief to 8 of the 25 patients complaining of substernal pain, but Jones emphasizes that in no case was the relief as regular as that noted in typical angina pectoris. Atropine or belladonna often afforded striking relief. Dyspnea was a frequent symptom in Jones's group and occurred in about one third of the patients with large hernias and one tenth of those with small ones. Palpitation was an occasional symptom.

Jones discusses the probable mechanism of causation of symptoms in these cases and concludes that when the hernia is large actual displacement of the heart and lungs may produce symptoms. A good example of this has recently been reported by McGinn and Spear.[72] Jones also believes it is logical to assume that the discomfort or pain is often secondary to intraesophageal or intragastric disturbances with typical referred pain and that the stimulus is mediated over visceral afferent fibers supplying the stomach or esophagus or over the sensory afferent fibers from the diaphragm.

We would like to emphasize the fact that both hiatus hernia and coronary heart disease may occur in the same patient, both being found in older persons, and in such patients they may be present together.

Thrombi in the Heart.—Garvin [73] studied the clinical and pathologic records of 771 consecutive autopsied patients who died of heart disease as to the occurrence of mural thrombi and infarction. Of the 771 patients, 265, of 34.4 per cent, had one or more mural thrombi. Thrombi were found in two thirds of the patients in whom myocardial infarction was present and in about one third of the patients with coronary artery disease without myocardial infarction or hypertensive or rheumatic

72. McGinn, S., and Spear, L. M.: Diaphragmatic Hernia Presenting the Clinical Picture of Acute Cor Pulmonale, New England J. Med. **224**:1014, 1941.

73. Garvin, C. F.: Mural Thrombi in the Heart, Am. Heart J. **21**:713, 1941.

heart disease. The incidence of mural thrombi was high (40-47 per cent) in patients with hypertensive and with coronary heart disease complicated by various other types of heart disease. The incidence was low in patients with cor pulmonale and with subacute bacterial endocarditis. In patients with rheumatic heart disease mural thrombi occurred two and one-half times as often when auricular fibrillation was present. In patients with hypertensive heart disease the incidence of mural thrombi was three times as high in those below 40 as in those above 60. In rheumatic heart disease the incidence of mural thrombi was much higher in the older patients.

Garvin [74] also studied the same group of patients with respect to mural thrombi and infarction of various viscera. He found that pulmonary infarction was almost three times as frequent in those patients with mural thrombi in the right side of the heart as in those without thrombi in this location. Also, infarcts of the brain, kidneys, spleen, intestines and/or extremities were more than twice as common in patients with mural thrombi in the left side of the heart as in those without thrombi in this area.

270 Commonwealth Avenue.

74. Garvin, C. F.: Mural Thrombi in the Heart as a Source of Emboli, Am. J. M. Sc. **201**:412, 1941.

News and Comment

Announcement of Fellowships in Medicine and Public Health.—The Commonwealth Fund of New York, a philanthropic foundation established in 1918 by the late Mrs. Stephen V. Harkness, announces that it is offering through the Pan American Sanitary Bureau fifteen fellowships for one year's study of public health subjects or postgraduate medical courses to properly qualified persons who are citizens of the other American republics. Fellowships in public health will be open to physicians, sanitary officers, technicians, public health nurses, etc. Fellows will be selected through a system of cooperation with medical and health authorities of the different countries concerned, and whenever it is deemed advisable they will be interviewed by traveling representatives of the Pan American Sanitary Bureau. Each fellowship will provide living allowances while the holder is in the United States, travel costs and tuition. Knowledge of the English language and the possession of certain specific qualifications will be among the requirements.

Application blanks giving complete information will be available through the Commonwealth Fund, 41 East Fifty-Seventh Street, New York; the Pan American Sanitary Bureau, Washington, D. C., or chiefs of American Missions in Latin America.

Proceedings of the Federation of American Societies for Experimental Biology.—The Federation of American Societies for Experimental Biology, composed of the American Physiological Society, the American Society of Biological Chemists, the American Society for Pharmacology and Experimental Therapeutics, the American Society for Experimental Pathology, the American Institute of Nutrition and the American Association of Immunologists, began publication of the federation proceedings in 1942.

Four issues will be published annually. Each year the March issue will contain the complete program of the scientific sessions of all the component societies as prepared for the forthcoming annual meeting of the federation, with abstracts of all scientific papers to be presented; the June and the September issue will contain the full text of twenty or more papers presented at the annual meeting, including probably the papers on the joint society program and papers of several society symposiums, and the December issue will contain material pertinent to the membership of the federation, i. e., the officers and a membership list, together with an index of the completed volume.

The subscription price is $4 ($4.75 foreign), payable in advance. Subscriptions should be sent to Dr. D. R. Hooker, Managing Editor, 19 West Chase Street, Baltimore.

Eighth Annual Meeting of the Mississippi Valley Medical Society.—The eighth annual meeting of the Mississippi Valley Medical Society will be held in the Hotel Lincoln-Douglas, Quincy, Ill., September 30 and October 1 and 2. The program will be given by twenty-five clinician teachers who will present over forty lectures, demonstrations, instructional courses, etc. On September 30 there will be a series of instructional courses by Kansas City clinicians and a complimentary stag supper. On October 1 a group of well known Chicago teachers will have charge. A special physicians' sports event program will be featured on

this date, with prizes for golf, skeet, bowling, archery and horseshoes. The banquet will be addressed by Dr. Edward H. Cary, of Dallas, Texas, past president of the American Medical Association, and the presidents of the state medical societies of Illinois, Iowa and Missouri. There will be numerous technical and scientific exhibits. Every ethical physician is cordially invited to attend, and no registration fee will be charged physicians in the uniforms of the armed forces of the United States. The complete program will appear in the September issue of the *Mississippi Valley Medical Journal*, and further information may be secured from the secretary of the society, Harold Swanberg, M.D., W. C. U. Building, Quincy.

Meeting of the Medical Editors at Quincy, Ill., September 30.—The second annual meeting of the Mississippi Valley Medical Editors' Association will be held at the Hotel Lincoln-Douglas, Quincy, Ill., the evening of Wednesday, September 30. This will be a dinner meeting under the leadership of Dr. Clyde P. Dyer, of St. Louis, editor of the *St. Louis County Medical Bulletin* and president of the Mississippi Valley Medical Editors' Association. All past and present medical editors and those persons interested in medical journalism or medical writing are cordially invited to attend. There is no registration fee. The program of the meeting or dinner reservations may be secured through Dr. Harold Swanberg, secretary of the association, W. C. U. Building, Quincy.

American Association for the Advancement of Oral Diagnosis.—The ninth annual congress of the American Association for the Advancement of Oral Diagnosis will be held in Boston November 12 and 13 at the Forsyth Dental Infirmary.

The subject of this year's congress will be "The Military Aspects of Oral Diagnosis."

Members of the medical and the dental profession in the United States and the countries of the Western Hemisphere who are interested are cordially invited to attend and may obtain programs by communicating with the secretary, H. Justin Ross, 515 Madison Avenue, New York.

Book Reviews

Arthritis and Allied Conditions. By Bernard I. Comroe, A.B., M.D., F.A.C.P. Second edition Price, $9. Pp. 878. Philadelphia: Lea & Febiger, 1941.

The appearance of a second edition of Comroe's book on arthritis a short time after the publication of the first edition attests to the value of the work. It apparently has been well liked by the reading medical world and has proved of worth to students, to practitioners and to specialists in the field of arthritis. It is rather refreshing, parenthetically, to have a book of this character emanating from the pen of a man who is fundamentally an internist rather than an orthopedist.

The new edition has undergone a complete revision. Although arthritis seems to be more or less of a static condition, a considerable number of new thoughts, suggestions and practices have evolved in the last few years, all of which are incorporated and discussed in the book. Incidentally, forty additional illustrations have been added to the volume.

This new edition follows closely the general plan of the first edition. Three introductory chapters deal with the general features of arthritis, and then follows a series of chapters on rheumatoid (atrophic) arthritis. Starting at page 59, rheumatoid arthritis in all its many aspects, although largely treatment, occupies nearly the next three hundred pages. To degenerative joint disease (osteoarthritis) are assigned two chapters. Succeeding this are divisions devoted to spondylitis, fibrositis, radiology, rheumatic fever, gonorrheal arthritis, tuberculosis and syphilitic joint disease, traumatic arthritis and gout, as well as several others. Chapter 43 deals with the painful shoulder, really by no means an expression of arthritis, but nevertheless it does seem appropriate to incorporate it in this book, as well as chapters 44 and 45, on painful feet and on backache. The last chapter of the book deals with the sulfanilamide compounds. There is a question in the mind of the reviewer whether there is any necessity of incorporating such a chapter in a book devoted to arthritis; certainly extremely rarely is there any indication for the administration of one of these compounds in the treatment of arthritis, surely not of the ordinary and common form of the disease to which so many chapters are devoted. One other criticism that might seem legitimate is the rather poor arrangement of the chapters. It might be advisable to put the ones on radiology and arthritis, the organization of a clinic for arthritic patients and several others in the early part of the book, which represents a more or less general discussion of the problems of arthritis, then systematically follow through with those devoted to the various types of the disease. In discussing the treatment of rheumatoid arthritis the author gives the usual physical method of treatment, then adds a chapter which has to do largely with the use of neoarsphenamine, acetylsalicylic acid and iodides and the treatment of associated anemia; then follows a chapter on vaccines, succeeded by one on the orthopedic management of arthritis, which certainly should be incorporated with the discussion of physical measures.

The book, even if not well organized, is carefully and thoughtfully written. The illustrations are commendable, and the boxed incorporated summaries are advantageous to students or to rapid readers. The format of the book is excellent, as would be expected from its publishers.

La enfermedad reumatica. By Domingo Urrutia M. and Samuel Vaisman B. Pp. 191, with graphs, diagrams, photomicrographs and electrocardiograms. Santiago de Chile: La Sud-America, 1941.

The impetus initiating this monograph was derived from a realization that rheumatic heart disease is an enormous public health problem. The authors are members of the department of clinical medicine of the University of Chile, and it was published under the auspices of the Direccion General de Sanidad y El Departmento Central de Madre y Nino.

The monograph is written principally for practitioners of medicine in Chile, particularly for those in the remote provinces. It is an orderly discussion of rheumatic heart disease, starting with its social significance and relating the etiology, the pathology, the clinical aspects, the laboratory data and the treatment of the disease.

In preparing their discussion the authors have reviewed and briefed most of the recent publications on the subject. Their main sources have been from the United States of America and Great Britain, though some are from Germany, France and South America. In all, they reviewed seventy-one publications. They also have included their own observations based on a series of 285 rheumatic children treated during the last five years by the department of student health of the University of Chile, 5,000 students treated during the last five years in Santiago and on 430 hospitalized patients treated over a ten year period in the university, as well as a review of 13,144 autopsy reports compiled since 1919 by members of the pathology department of the university.

It is interesting to note that their results to date closely simulate those reported from similar latitudes in the northern hemisphere.

The monograph is bound in paper; reading is facilitated by large type, titles and subtitles in bold-faced print and a résumé in bold-faced print at the end of each chapter.

Acute Alcoholic Intoxication: A Critical Review. By Henry W. Newman, M.D. Price, $2.50. Pp. 207. Stanford University, P. O., Calif.: Stanford University Press, 1941.

Dr. Henry W. Newman, assistant professor of medicine (neuropsychiatry) of Stanford University Medical School, is well qualified to discuss the problem of acute alcoholic intoxication, as shown by his numerous publications on this subject during the past ten years.

The book is not intended to review in detail all of the literature but instead is designed to present the major contributions of the last few years which add to the scientific and fundamental understanding of the subject.

The contents are divided into two parts; the first deals with the general actions of ethyl alcohol, namely, the absorption and distribution, the excretion and the combustion of this substance. This section brings together many scattered reports from the literature and presents them as individual points of view.

The second part deals with the toxicology of ethyl alcohol, namely, the acute toxicity of this substance, the chemical diagnosis of drunkenness and the treatment of acute alcoholic intoxication. This section, perhaps the most valuable part of the book, presents the results of work on many original problems which have practical value in the medicolegal practice of medicine. The practical application of tests for drunkenness is described in detail. The research concerning the problem of acute intoxication and that concerning the operation of motor vehicles was carried out by the author in collaboration with the California Department of Motor Vehicles in an effort to improve legislation regarding drunken driving.

The book contains a compilation of original work done by the author and other investigators. Their experimental results are presented, and the conclusions are left for the reader to draw.

Personality and Mental Illness. By John Bowlby, M.D. Price, $2.75. Pp. 288, with charts. New York: Emerson Books, Inc., 1942.

This interesting study deals with personality traits which when exaggerated lead to recognizable psychotic states. The author's point is that physchoses are more quantitative than qualitative deviations from a person's previous status. The material is well handled and written in excellent style; it makes interesting and convincing reading.